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A Monthly Journal Devoted to the Art
and Science of Surgery

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VOLUME 17
JANUARY—JUNE, 1945

ST. LOUIS
THE C. V. MOSBY COMPANY

1945

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Printed in the
United States of America

Press of
The C. V. Mosby Company
St. Louis

SURGERY

VOL. 17

JANUARY, 1945

No. 1

Original Communications

TRAUMATIC PERFORATION OF THE COLON AS SEEN IN A GENERAL HOSPITAL

MAJOR BENTLEY P. COLCOCK, MEDICAL CORPS, U. S. ARMY

THE mortality rate following traumatic perforation of the colon in World War II has dropped to the neighborhood of 33 per cent. This represents a marked improvement over the mortality figures for World War I, which, in this type of patient, ranged from 50 to 75 per cent, and is largely due to the early replacement of blood loss by plasma, and particularly whole blood, the intraperitoneal use of the sulfonamides, and the excellent surgery being done by the well-trained abdominal surgeons in our forward field and evacuation hospitals.

That an uncomfortably high morbidity still exists in this group of cases is not generally appreciated except by those surgeons working in the general and other hospitals back of the forward areas. Few of the patients treated here recover without some type of complication such as wound infection, wound separation, retraction of the colostomy, evisceration, or the development of abdominal wall, intra-abdominal, subphrenic, and retroperitoneal abscesses. Most of them have a prolonged convalescence extending over a period of two or three months. After this period of convalescence, many have to be evacuated to the zone of the interior for major intra-abdominal surgical procedures to restore intestinal continuity. These additional procedures are associated with an accepted mortality rate of from 8 to 10 per cent. The ingenuity of the surgical staff is frequently taxed to the utmost in order to prevent certain complications from progressing to a fatal termination. It is my considered opinion that with further experience and particular attention to certain details in the primary treatment of these patients, the reduction in the mortality rate can be followed by a corresponding reduction in the morbidity rate.

The following suggestions are made on the basis of a rather extensive experience with the Mikulicz procedure in the treatment of carcinoma of the colon in civilian life, modified by the experience gained from the

Received for publication, June 9, 1944.

study and care of a group of twenty-three patients with traumatic perforation of the colon who had been evacuated to North Africa from the Italian theatre of operations.

The fundamental principles concerning the treatment of battle casualties with perforation of the colon must first be stated: (a) It is generally accepted today that the safest method of dealing with a laceration of the colon is by exteriorization of the lacerated segment of bowel. (b) The primary object in the treatment of these patients in the forward area is the saving of life, and the setting up of conditions which will facilitate the further care of that patient is secondary. The facts and the problems confronting the surgeon in the forward area have been kept in mind at all times in the following discussion, although, as already pointed out, the secondary complications occurring in these patients may be sufficiently grave so as to actually jeopardize the life of the patient.

The most important step in the exteriorization of the colon is the adequate mobilization of the bowel. In the first place, this greatly facilitates the exteriorization of the entire injured segment. It must be kept in mind that frequently a considerable area of bowel wall surrounding the actual perforation has been devitalized by the trauma, and will subsequently slough. It is equally important that the entire injured area must be exteriorized without tension. If tension on the bowel is necessary to bring the segment above the skin level, it will inevitably retract. If this retraction stops at the skin level nothing more serious than a constricted colostomy stoma may result. This often functions poorly, and renders the subsequent examination and clamping of the spur much more uncomfortable for the patient. If the retraction proceeds below the skin level, it leads to infection of the wound with partial or complete separation. This, in turn, may lead to evisceration. If the retraction extends below the peritoneal level as in one of our patients, local or generalized peritonitis results with the frequent formation of intraperitoneal, pelvic, or subphrenic abscesses. In seven of our patients the colostomy stoma was at the level of the skin or beneath. Five of these men had abscesses in the abdominal wall with partial or complete separation of the abdominal incision. Two developed subphrenic abscesses (bilateral in one case), and one patient eviscerated. The operative notes occasionally mentioned the fact that tension was necessary to exteriorize the bowel.

The following brief résumé of the clinical course of one of these patients illustrates how a series of complications occurred, each of which almost cost the patient his life. A few more minutes spent on mobilization of the colon might have prevented these complications.

A soldier was wounded in the left flank, Nov. 3, 1943, by enemy shell fragments. Fortunately, due to the proximity of a field hospital, he was operated upon within three hours after his injury. Through a left posterolumbar incision, thirteen perforations of the ileum and jejunum were closed and four inches of the

descending colon removed because of two perforations at that point. There was not sufficient mobility present for exteriorization through an anterior stab incision, so the two loops of colon were brought out through the operative incision in the left flank. He was admitted to the general hospital, Nov. 13, 1943, with a temperature of 101° F., vomiting occasionally, but taking some liquids by mouth. His wound was completely separated, with the sutures lying loose in it. The colostomy loops had separated and retracted below the peritoneal level, exposing the dorsal musculature, the layers of the abdominal wall, and the adjacent peritoneal cavity to constant fecal contamination. The adjacent loops of small bowel were covered by granulation tissues. Fever continued and Nov. 29, 1943, a right subphrenic abscess was discovered and drained. (The predominant organisms were *Bacillus coli* and *Bacillus clostridia*.) He improved temporarily, but again became febrile, and his condition deteriorated. Sterile pleural effusion, 500 c.c., was aspirated from the right side of the chest, Dec. 3, 1943, and 900 c.c. of a similar amber-colored fluid was aspirated from each pleural cavity, Dec. 7, 1943. His temperature rose to 101 to 102° F. at night, pulse remained at 110 to 120, and his feet and back became edematous. Dec. 11, 1943, an abscess lying between the abdominal wall and the peritoneum, and extending medialward from the incision across the midline, was incised and drained (predominant organism again *B. coli*). He again became febrile after a short period of improvement. Dec. 16, 1943, 1,000 c.c. of clear amber-colored fluid were aspirated from the left pleural cavity and 750 c.c. from the right side. Dec. 22, 1943, a retrocecal abscess was drained of 200 c.c. of thick white pus. In spite of this, there was no essential change in his condition which continued critical. X-ray examination, Dec. 26, 1943, showed a small bubble beneath the left diaphragm, and a left subphrenic abscess was drained, but the patient again failed to make any permanent or sustained improvement. Jan. 6, 1944, pus was obtained from the left pleural cavity. It was loculated posteriorly and was drained by a thoracotomy. He now began to show the first definite and sustained improvement, but continued to have a low-grade fever. He was given 300,000 units of penicillin. (The sulfonamides had been discontinued long before because of their tendency to accelerate the fall in the red blood cell level, which was being sustained by repeated blood transfusions.) Possibly due to the penicillin, but probably to the fact that we had finally drained the last abscess, he continued to improve, his temperature fell to normal, and he became ambulatory by the time he was evacuated to the zone of the interior. His wound had finally healed but he will require a major intra-abdominal procedure to restore intestinal continuity because of the widely separated and retracted colostomy loops.

Mobilization of the large bowel by division of its lateral peritoneal attachments is a relatively avascular procedure. The only blood vessels which may need to be clamped and divided are a few at the splenic and hepatic flexures. After the line of fusion between the peritoneum covering the bowel and the lateral parietal peritoneum has been incised (see Fig. 1), the bowel and its mesentery are easily mobilized medialward by sharp and blunt dissection. This provides ample bowel for exteriorization of the proximal and distal loops, even if resection of several inches or more of bowel should be necessary. The retroperitoneal second portion of the duodenum will be encountered on the right side, and should be carefully reflected posteriorly. The ureter on the side involved, should, of course, be found and preserved. An excellent guide to the ureters is the spermatic vessels cross-

study and care of a group of twenty-three patients with traumatic perforation of the colon who had been evacuated to North Africa from the Italian theatre of operations.

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ing anterior to the ureter directly below the kidney pelvis and lying just lateral to it throughout its course down to the pelvis. These vessels are easily identified as the dissection proceeds medialward, and the ureter will be found 1 cm. or less further toward the midline (see Fig. 2B). In exteriorization of the splenic flexure, the jejunum at the ligament of Treitz will often be exposed and injury to it should be avoided. The mesentery of the colon will become rather thin and delicate as it is reflected from the posterior abdominal wall and care must be taken lest it be perforated by the retracting fingers. Any perforations should, of course, be closed to prevent possible herniation of small bowel through the aperture. Little, if any, dissection is usually necessary in liberation of the sigmoid colon. With wounds of the ascending

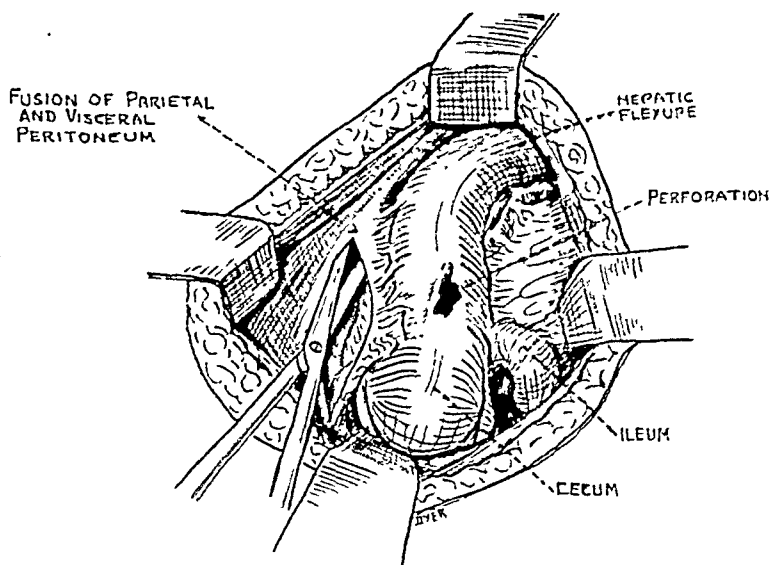


Fig. 1.—Showing the first step in mobilization of the right colon by incision of the peritoneum along the avascular line of fusion between the visceral and lateral parietal peritoneum.

colon, the hepatic flexure must be detached, and in the case of the descending colon, liberation of the splenic flexure in addition to the division of the lateral attachments will provide adequate mobilization (see Fig. 3). The amount of dissection necessary with wounds of the transverse colon depends largely on its redundancy. The omentum has an avascular attachment to the transverse colon and can be easily removed. Even the necessary liberation of both flexures should not prolong the operative procedure unduly in most cases and with the adequate exposure that is essential in these patients, it should add but five to ten minutes to the operating time. Because of the possibly increased risk of wound infection from the ileostomy, there is a question in the minds of some authorities as to whether it is safe to exteriorize the right colon and construct a double-barreled ileocolostomy by approximation of the terminal ileum to the ascending or transverse colon. This certainly can be done without increased risk of wound

infection when operating for carcinoma of the cecum and ascending colon in civilian practice. Two patients of this group had had a procedure of this type. One had no infection of his wound. The ileocolostomy had been clamped and closed, and he was returned to duty. A second patient had a moderate infection of his wound with separation of the skin and subcutaneous layers. The ileocolostomy had been

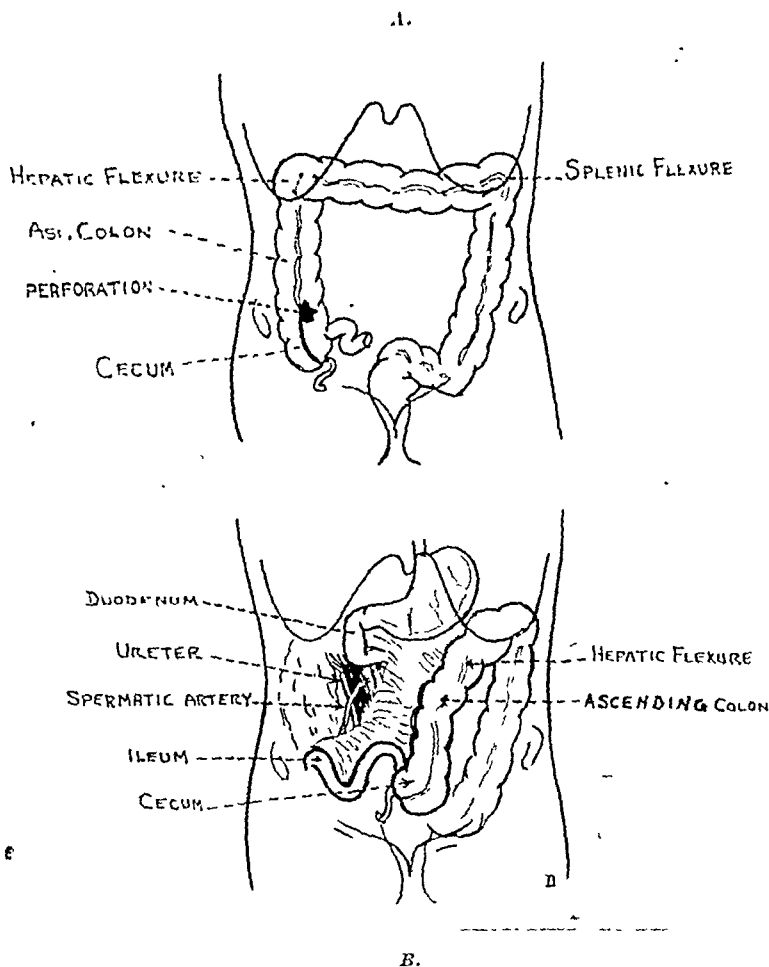


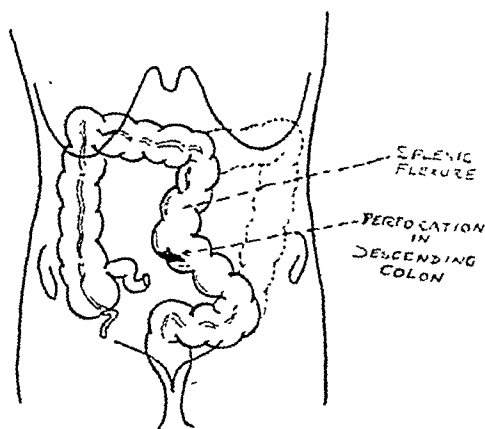
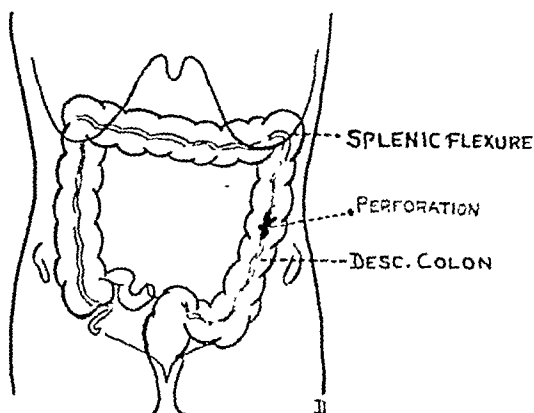
Fig. 2.—A, Schematic representation of a colon. B, Mobilization of the right colon, showing duodenum, right ureter, and right spermatic v from their anterior surfaces.

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clamped and closed without difficulty, and the abdominal wall is now in good condition. A third patient with extensive wound of the ascending colon had a right lower quadrant ileostomy and an epigastric transverse colon colostomy. The wounds healed perfectly, but he had to be evacuated to the zone of the interior with the added nursing care that an ileostomy requires. He still faces a major intra-abdominal procedure with an associated mortality between 5 and 10 per cent. Complete information on all of these cases involving the right colon cases will be required to settle definitely this point.

In the second place, adequate mobilization of the bowel permits the rapid formation of a five- or six-inch double-barreled colostomy spur (see Fig. 4). This, in turn, makes it possible to restore intestinal continuity at a later date, by a minor extraperitoneal procedure. Two rows of sutures uniting the two loops facilitate the subsequent clamping of the partition. If haste is imperative, one row of sutures is sufficient to prevent the small bowel or omentum from inserting itself between the loops of the spur, and the partition can be clamped without

A.



B.

Fig. 3.—A, Schematic representation of a perforating wound of the descending colon. B, Showing mobilization of the left colon by freeing the descending colon, splenic flexure, and the distal portion of the transverse colon.

risk (see Fig. 5). These sutures should not be passed into the lumen of the bowel. There is no tension of this suture line and approximation is all that is required. Uniting the longitudinal bands of the colon by seromuscular sutures tied without constriction of the tissue permits the formation of a double-barreled colostomy which involves no added risk from peritonitis, and which is ideal from the point of view of the

later restoration of intestinal continuity. A five- or six-inch spur not only permits the colostomy stoma to be brought well (one and one-half to two inches) above the skin level, but also insures an adequate bowel lumen after the subsequent closure (see Fig. 6). There will be no post-operative leakage of intestinal content if the spur is made of sufficient length in the first place and the bowel wall is rendered sufficiently

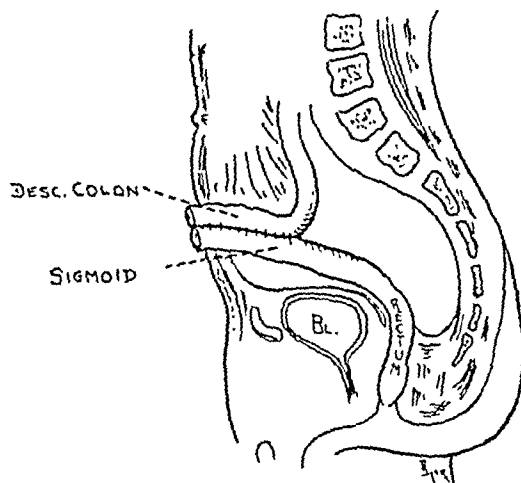


Fig. 4.—Schematic Sagittal view of the construction of a double-barreled colostomy spur for a perforation low in the sigmoid colon. This may necessitate mobilization of the upper rectum and rectosigmoid portion of the colon.

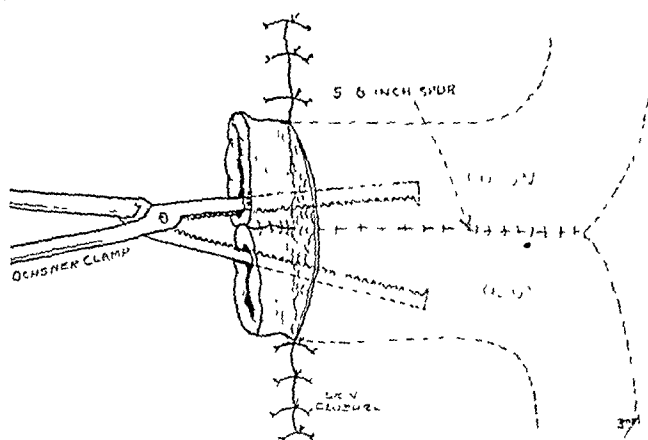


Fig. 5.—Schematic representation of the colostomy spur, and the application of the straight Ochsner clamp. It will usually require two or three applications of the clamp for complete division of the spur.

pliable by removal of all scar tissue at the time of closure, so that it can be inverted without tension. It was possible, by slow and careful clamping of the partition, to secure sufficient lumen to permit extra-peritoneal closure in approximately 50 per cent of our patients, although only a few had approximation (by sutures) of the two loops at the time of the original operation. Three other patients were evacu-

ated because of unhealed osteomyelitis of the sacrum, and one because the two loops were crossed, making it impossible to clamp the partition without destroying the blood supply to the bowel. No complications occurred which could be attributed to the clamping or closure, and there has been no mortality among our patients with perforated colons. One patient had leakage of intestinal content postoperatively, which was probably due to the combination of a short spur, plus the formation of an abscess postoperatively in the old sinus tract made by the shrapnel fragment, which communicated with the wound of closure.

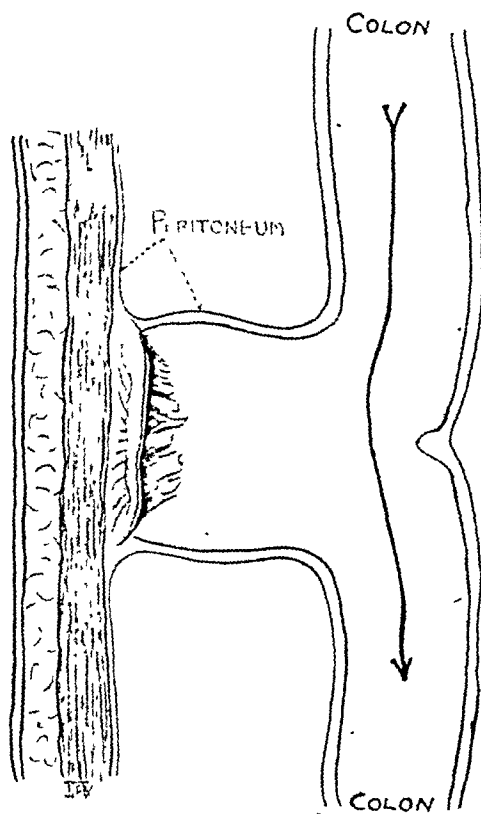


Fig. 6.—Schematic representation of the intestinal lumen following closure. The peritoneal cavity has not been opened, and the muscle, fascia, and skin layers of the abdominal wall have been approximated over the inverted colostomy stoma.

(Those patients whose colostomies have been closed have been returned to Class B duty in this theatre of operations. Several, who were technical sergeants, have been returned to work similar to that carried on before their injury.) More of the colostomies could have been closed and the patients returned to duty, and the subsequent care in the group that was salvaged would have been rendered infinitely safer and easier had it been possible to construct an adequate double-barreled spur at the time of the original operation.

The incidence of infection in these wounds is high, because we are dealing with an open wound in the colon, frequently associated with

gross soiling of the peritoneal cavity by fecal material. Because of this fact, some surgeons have felt that complete closure of the laparotomy incision with exteriorization of the bowel through a lateral stab wound decreases the incidence of infection and separation. In the original incisions in our small series, the incidence of infection was equal (5 per cent) in the group with the stab wound colostomy and in the group with the colostomy in the laparotomy incision. Whether the additional time and manipulation required in the former group are justified remains to be settled when the collected statistics from all hospitals are analyzed. This is also true of other impressions of ours, such as the advisability of the use of through-and-through sutures without closure of the wound in layers. It is certainly important that these patients should have a minimum of transportation, not only until they have passed the critical stage, but until they have good wound healing. Certainly it is true that any and all measures designed to decrease contamination and to achieve primary healing of the incision are to be commended because infection with the frequently associated separation of the wound markedly prolongs the convalescence of these patients.

The following is an illustrative case.

A 28-year-old artilleryman sustained a penetrating wound of the left side of his abdomen, Nov. 11, 1943. At operation, four hours later, a wound of the jejunum was found and closed, a wound of the splenic flexure of the colon was exteriorized, and a retroperitoneal hematoma drained. In order to provide more adequate exposure, a transverse incision was added to the left rectus incision. A wound infection developed and on the fourteenth day, after coughing, he eviscerated. Following closure, he began to show evidence of a more serious infection, with necrosis of the adjacent tissues of the abdominal wall. A micro-aerophilic streptococcus was found which responded to zinc peroxide, but much of the abdominal wall was lost and the colostomy retracted below the skin level.

Dec. 20, 1943, he was admitted to a general hospital in fair condition, with a large granulating wound, nine by six inches, oval in shape. The colostomy, just to the left of the wound, was below the skin level, but was functioning well. There was a purulent discharge from a sinus tract just lateral to the colostomy. Temperature was 101° F. Dec. 29, 1943, a retroperitoneal abscess was drained through the left flank. The patient improved temporarily, but again became febrile, with a deterioration in general condition. Jan. 2, 1944, a posterior right subphrenic abscess was drained through the bed of the twelfth rib. He immediately began to improve and his temperature dropped to 100° F. Jan. 5, 1944, he disrupted the large granulating abdominal wound, and eviscerated for the second time. The stomach, several feet of small bowel, and the transverse colon were replaced in the abdominal cavity and the wound closed under considerable tension. After a critical period of two or three days he gradually rallied, but the wound partially separated, and on Jan. 12, 1944, he developed a high jejunal fistula in the center of the granulating area. In spite of various temporary measures designed to by-pass the jejunostomy, the opening in the bowel became larger and his condition again became critical. March 10, 1944, the fistulous area in the jejunum was resected and end-to-end anastomosis performed; a fourth attempt to close the abdominal wall was carried out. The colostomy, which was situated at the margin of the wound, was moved further into the flank to facilitate closure

and to decrease the subsequent contamination of the incision. The closure was partially successful due to necrosis and slough of the wound margins in the central portion, but the fistula has remained closed, and the patient is making satisfactory recovery at the time of this report.

The tremendous amount of supportive treatment necessary to carry these patients over each of their complications has not been mentioned, but can readily be imagined. The technical treatment of many of their complications is usually not difficult, but the diagnosis is often exceedingly difficult. These patients have all been through so much that their margin of safety is small and one must be constantly on the alert to detect even slight changes in their general condition. A slight elevation in a temperature curve which has been falling may indicate a new abscess which must be found and drained quickly, for it may be just "the straw which breaks the camel's back."

Thanks to the technical skill of the surgeons operating in the forward areas, it is now possible to state that the majority of patients sustaining a perforating wound of the colon will survive. We feel that before long it will also be possible to state that the majority of these patients will not have to be evacuated to the United States, but can be restored to useful duty in the theatre of operations, with no increase in the over-all mortality rate.

CONGENITAL ABSENCE OF THE GALL BLADDER

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ROCHESTER, MINN.

INTERESTING findings in a case of congenital absence of the gall bladder observed recently at the Mayo Clinic prompted a study of all of the cases of this anomaly that have been observed at the clinic and a review of the cases that have been reported in the literature. The cystic duct also was absent in most of the cases which form the basis of this report. This was the only concomitant anomaly of the extrahepatic bile ducts that was present in any of the cases. Anomalies of the extrahepatic bile ducts constitute another problem. They usually are found in stillborn infants or in infants born with icterus. They frequently are associated with other anomalies.

Many of the reports of congenital absence of the gall bladder were found to be inadequate for study. Many older reports consist only of statements that were made before some society.^{1,2} In some articles that otherwise were satisfactory, there was no mention of the status of the extrahepatic bile ducts and in some cases in which the anomaly was found at operation there was no means of ruling out the presence of an intrahepatic gall bladder. In an occasional report, the author mentioned having seen several other cases but did not describe the findings.

In 1902, Gay³ reviewed nineteen cases of congenital absence of the gall bladder that had been reported in the literature. Buddy⁴ and Theodor⁵ surveyed the German literature and the latter author reported a case which he had observed personally. Bower,⁶ in 1928, collected thirty-five cases from the literature and in four of these cases the cystic duct was present. He also reported a case which he had observed. Gross,⁷ in reporting a case of double gall bladder, in 1936, reviewed the literature on congenital anomalies of the gall bladder and summarized the findings in thirty-eight cases that had been reported since 1905. One may add the cases of Danzis,⁸ Fowler,⁹ Theodor,⁵ Torrance,¹⁰ and Whipple¹¹ to those mentioned by Gross.⁷ In addition, Whipple mentioned two other cases which he had observed previously. Since 1936, thirteen additional cases have been reported¹²⁻¹⁷ but reports of two of these cases were not available to us.¹⁸⁻²⁰ Thus, we were able to obtain thirty satisfactory reports that were made before 1900 and fifty that have been made since that time. To these cases that have been reported in the literature, we wish to add ten cases that have been observed at the Mayo Clinic.

Received for publication, June 2, 1944.

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The embryology of the gall bladder has been described adequately by Keibel and Mall.²¹ Two theories have been advanced to explain congenital absence of the gall bladder.⁷ The first of these is that the anomaly is due to failure of the gall bladder bud to develop from the hepatic diverticulum. This failure also would result in an absence of the cystic duct. The second theory maintains that the anomaly is due to failure of the gall bladder bud to resolve from its solid embryonic stage. The presence of a solid cord residue would favor the latter theory.

From comparative anatomy one learns that in the *Petromyzon*, the pigeon, and the rat the gall bladder diverticulum is present but disappears as the embryo matures. There are conflicting reports on the presence of the gall bladder in some species of animals. It probably is reasonable to assume that the gall bladder usually is absent in these species, which include the giraffe, the camel (?), and the elephant (?).^{2, 16} According to Mentzer,^{22, 23} the gall bladder has been said to be absent uniformly in twenty-six species of mammals including the goat, deer, rat, rhinoceros, peccary, pilot whale, hyrax,²⁴ two-toed and three-toed sloth, and the horse, ass, and mule, seventeen species of fish including the *Petromyzon* or the lamprey, which is a cyclostome, and nine species of birds including the dove and pigeon. It is interesting to note that, with the exception of the pilot whale, the mammals which normally do not have a gall bladder are predominantly vegetarian and depend on ingested carbohydrate for their body fat.

Many of the reports of cases of congenital absence of the gall bladder that appeared before 1900 were rather cursory and the cases differ from those reported since 1900. Such data as are available will be presented briefly. In twenty-four of the thirty cases the anomaly was found at necropsy; in two of the cases it was found at operation and confirmed at necropsy, which followed closely; while in four cases it was not stated whether the anomaly was found at necropsy or at operation. In five of the twelve cases in which an adequate history was obtainable, symptoms suggestive of cholecystic disease were present. Jaundice was present in six cases. The common duct was found to be dilated in five of the ten cases in which the size of the duct was mentioned. The cystic duct was present in four cases and noted as absent in thirteen cases. Stones were found in two cases. Twelve of the patients were females and ten were males. Eight infants were included, while in ten cases the patients were more than 45 years of age. Many of the cases in which the patients were infants were eliminated because of extensive associated anomalies.²⁵

The reports that have appeared since 1900 are more complete than those which were made previously. The anomaly definitely was stated to have been found at operation in two of the thirty cases reported

prior to 1900, but it was discovered in this manner in thirty-four of the sixty cases* reported subsequently. An element of doubt is introduced when the anomaly is observed at operation, but in six of the cases in which the anomaly was observed in this manner it subsequently was confirmed at necropsy. In this study we did not include cases in which a small pouch was seen on the common duct. In a few cases (for example, in the one reported by Miller),²⁶ there was a nubbin of the common bile duct which contained a stone. These cases were eliminated from consideration because of the likelihood that the nubbin represented the end result of inflammatory obliteration.

ANALYSIS OF CASES REPORTED SINCE 1900

Of the cases of this anomaly that have been reported since 1900, fifty were found satisfactory for study. To these fifty cases we wish to add ten cases which have been observed at the clinic. These cases will be reported briefly in this paper.

In twenty-six of the sixty cases the anomaly was found at necropsy and in the thirty-four remaining cases it was found at operation. In six of the thirty-four cases the presence of the anomaly subsequently was confirmed at necropsy. In the twenty-six cases in which the anomaly was found at necropsy, the following causes of death were mentioned: tuberculosis in five cases, lobar pneumonia or bronchopneumonia in five cases, and myocarditis in two cases. Syphilis was present in one case. As previously stated, in twenty-four of the thirty cases that were reported prior to 1900 the anomaly was found at necropsy. In five of these cases death was attributable to tuberculosis and in four cases it was due to pneumonia. It is evident that tuberculosis and pneumonia caused death in about the same percentage of cases in each group.

In twenty-four of the sixty cases the anomaly was found in the course of operation for suspected cholecystic disease. On four occasions it was disclosed by an exploratory laparotomy; in two cases a diagnosis of appendicitis was considered, and in four cases the anomaly was an incidental finding in operations on the stomach and duodenum.

The average age of the patients was 46.7 years. Forty-two of the patients were more than 45 years of age and four were less than 1 year of age. Thirty-six of the patients were females and twenty-three were males. In one case the sex of the patient was not mentioned.

Symptoms suggestive of cholecystic disease were present in thirty-five cases (in eight patients pain extended to the left side of the thorax and to the scapula). In thirteen cases the symptoms were not referable to the gall bladder and in twelve cases the symptoms were not described adequately. Jaundice was present in twenty-nine cases.

*This figure includes ten cases which have been observed at the Mayo Clinic.

In fifteen cases cholecystography failed to produce visualization of the gall bladder. Stones were seen in the region of the common bile duct in four cases.

The gall bladder fossa in the liver was present in seven cases and absent in twenty-five. It was not mentioned in twenty-eight cases. The cystic duct was present in four cases and absent in forty-two cases. It was not mentioned in fourteen cases. The common bile duct was dilated in nineteen cases and of normal size in twenty cases. In twenty-one cases mention of the size was omitted. In one of the cases there was a carcinoma of the common bile duct¹⁵ with dilatation of the duct above the lesion.* Gallstones were found in the common bile duct or in the hepatic ducts in sixteen cases. Their absence was mentioned in nineteen cases, but not mentioned in twenty-five cases.

The liver was noted as enlarged in nine cases and as cirrhotic in thirteen cases. Hepatitis was noted in five cases and the left lobe was absent in one patient. An unusually small quadrate lobe was seen in six cases. The pancreas was mentioned in twelve cases. Pancreatitis was present in eleven cases. The pancreas was poorly developed in one patient and diabetes was present in four cases. No mention was made of changes in the spleen.

The sixty cases may be divided roughly into three groups. One group consists of cases in which the patients were infants. In this group the absence of the gall bladder was noted at necropsy. Jaundice was a common finding and the causes of death were described as "emaciation," bronchopneumonia, peritonitis, encephalitis, and an imperforate anus. In the second group of cases the patients were between infancy and 45 years of age and the anomaly usually was found at necropsy. Death frequently resulted from pulmonary disease. In 73 per cent of the cases in which the patients were past the age of 45 years, symptoms similar to those found in cholecystic disease were present. In the majority of the cases in the last group the anomaly was discovered at operation.

REPORTS OF CASES OBSERVED AT THE CLINIC

CASE 1.—A Norwegian woman, aged 61 years, had had attacks of jaundice, chills, fever, and pain in the left upper quadrant of the abdomen which had extended to the left scapula. Abdominal distress and belching had occurred after meals. These symptoms had been present for eight years. Cholecystography revealed nonfunctioning gall bladder. The value for the serum bilirubin was 6.5 mg. per 100 c.c. Analysis of the gastric contents disclosed an absence of free hydrochloric acid; the value for the total acidity was 6 according to the method of Töpfer. Cholecystic disease and biliary obstruction were suspected. Operation disclosed absence of the gall bladder and cystic duct. There was no gall bladder fossa in the liver. Three stones were found in the dilated common bile duct.

*Although the term "common bile duct" implies fusion of the cystic and hepatic ducts, it is used here to designate fusion of the hepatic ducts also. In two of the cases, two hepatic ducts proceeded independently into the duodenum. This may have been true in more cases but missed at operation.

A T tube was inserted into the common bile duct. The pancreas and liver were normal. The jaundice disappeared rapidly and the concentration of serum bilirubin decreased to 1.2 mg. per 100 c.c. in two weeks. The T tube was removed in two months. The patient was asymptomatic thereafter.

CASE 2.—A man, aged 68 years, of Norwegian descent, had had attacks of jaundice and of epigastric pain which extended to the sternum. These attacks had been present for six weeks and morphine had been required. Other symptoms included fever and chills, intolerance of fat, and a loss of sixty pounds (27.2 kg.). No jaundice was present at the time the patient was examined. The value for the serum bilirubin was 1.1 mg. per 100 c.c. Cholecystography did not reveal any gall bladder. Obstructive cholecystic disease was suspected. Operation revealed absence of the gall bladder. The common bile duct was of normal size and no stones were present. The liver was normal but pancreatitis, grade 3 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition), was present. A T tube was placed in the common bile duct. Recovery was excellent. After slow progressive clamping of the tube without symptoms being produced, the tube was removed two years after its insertion. A year later the patient was still asymptomatic.

CASE 3.—A woman, aged 29 years, of Norwegian descent, had colicky pain in the left side of the epigastrium, fever and chills for four years. Ingestion of food or vomiting had relieved the symptoms. She had lost twenty pounds (9.1 kg.). Roentgenologic examination of the stomach revealed a duodenal ulcer and a subacute perforating gastric ulcer. Operation disclosed hourglass stomach, two gastric ulcers, and a duodenal ulcer. Absence of the gall bladder was noted incidentally. The common bile duct was normal. A gastric resection was performed. Recovery was uneventful. Four years after resection the patient was well.

CASE 4.—A woman, aged 39 years, of Irish descent, had had attacks of gaseous distention, nausea, and vomiting which had been precipitated by ingestion of fatty foods. These attacks had been present for three years. There was pain in the right side at the level of the umbilicus. Jaundice was not present. Roentgenologic examination of the stomach did not disclose any abnormality. Disease of the gall bladder was suspected. Operation disclosed absence of the gall bladder and cystic duct. The common bile duct was moderately dilated but it was not explored. The position of the duct was normal. The appendix was removed and the pathologist reported the presence of catarrhal appendicitis. Two years later the patient stated that the symptoms still were present.

CASE 5.—A man, aged 53 years, had had pain in the upper part of the abdomen and bloating after meals for ten years. The pain had been most intense in the left subcostal region. Tenderness had been noted over the right upper quadrant of the abdomen. Some of the symptoms had been relieved by taking bicarbonate of soda. On many occasions, morphine had been required to relieve the pain. There had not been any jaundice or vomiting. Although roentgenologic examination of the stomach disclosed a duodenal ulcer, a diagnosis of cholecystic disease was considered. Operation disclosed absence of the gall bladder. The appendix had been removed previously. A duodenal ulcer was present. The gall bladder fossa in the liver was present and the common bile duct was of normal size. A posterior gastroenterostomy was performed. The patient returned four, and again seven years, after the operation. On each of these occasions, he complained of persistence of symptoms. He stated that the symptoms had not been relieved by food or bicarbonate of soda. Roentgenologic examination of the stomach revealed a properly functioning gastroenteric stoma and there was no evidence of ulceration.

CASE 6.—A woman, aged 52 years, of Scotch descent, had suffered from pain in the epigastrium and left costal margin for four years. The severity of the pain had increased when the patient had lain down; the pain had not related to the ingestion of food except that there was marked intolerance to fat. She also complained of attacks of colicky pain which was situated in the upper part of the abdomen and extended upward to the left side of the thorax. Nausea and vomiting also had been present. An attack which had occurred one month before the patient came to the clinic had been associated with jaundice, pruritus, chills, fever, and acholic stools. There also had been an attack of "bloody" diarrhea. It was believed that the patient had cholecystitis with cholelithiasis. Cholecystography revealed a nonfunctioning gall bladder. Operation disclosed absence of the gall bladder. The common bile duct was normal and no stones were palpable. The liver was normal but chronic pancreatitis was present. No other operative procedure was employed.

CASE 7.—The patient was a man, aged 57 years, who was a Canadian. For twelve years he had had attacks of colic in the right upper quadrant of the abdomen and morphine had been required to relieve the pain. The attacks had been associated with nausea, vomiting, chills, fever, and mild jaundice. Six months previous to his registration at the clinic he had noticed the pain in the left upper quadrant and the development of a mass in that region. Roentgenologic examination revealed a mass attached to the stomach. The colon was normal. Exploratory laparotomy revealed a lymphosarcoma of the stomach and absence of the gall bladder and cystic duct. The gall bladder fossa in the liver was present. The common bile duct, liver, and pancreas were normal. The malignant lesion was not removed. The patient died eleven months later.

CASE 8.—A man, aged 74 years, of English descent, was found to have no gall bladder at necropsy. In 1918, he had had persistent, severe backache. In 1924, he had complained of severe epigastric distress. A diagnosis of diabetes had been made and a tentative diagnosis of hemochromatosis had been verified by skin biopsy. Examination had disclosed splenomegaly and an enlarged liver. Roentgenologic examination of the stomach had not disclosed any abnormality. In 1926, he came to the clinic because of periumbilical pain of recent origin. His appendix was removed because of subacute appendicitis. He continued to complain of pain in the upper part of the abdomen. He died in 1940 of diabetes, and necropsy disclosed absence of the gall bladder. The liver and pancreas were normal and there was no evidence of bronzing. The gall bladder fossa also was absent. The common bile duct was normal and no stones were present.

CASE 9.—A man, aged 38 years, of Danish descent, at necropsy was found to have no gall bladder. He registered at the clinic because of progressive weakness and loss of strength. The symptoms were too involved to permit one to judge whether they were referable to the biliary tract. Necropsy disclosed milary tuberculosis, ileal tuberculosis, tuberculous lymphadenitis, tuberculosis of the left suprarenal gland, bronchopneumonia, pernicious anemia, and left hydrothorax. The common bile duct was normal but the cystic duct was absent. The liver and pancreas were normal.

CASE 10.*—A woman, aged 50 years, of Finnish descent, had had attacks of pain in the epigastrium which had been associated with jaundice, pruritus, acholic stools, choluria, and dietary intolerance to fat. Morphine had been required for relief of pain. She also had had symptoms of hyperthyroidism. Palpation revealed a nodular enlargement of the thyroid gland. The basal metabolic rate was +32 per cent. There was tenderness in the epigastrium, and icterus was noticed.

*This is the most recent case that has been observed at the clinic.

Cholecystography did not disclose any gall bladder. Thyroidectomy was performed. Pathologic examination disclosed parenchymatous hypertrophy of degenerating fetal adenomas in a colloid thyroid gland. Two months later exploratory laparotomy disclosed absence of the gall bladder and the cystic duct. There was marked distortion of the second and third portions of the duodenum. The common bile duct was located with difficulty and was situated somewhat posteriorly to the usual site. It was thickened and dilated one and one-half times its normal diameter. No stones were found. There was no gall bladder fossa in the liver but hepatitis, grade 2, and pancreatitis were observed. A T tube was inserted in the common bile duct to be left for more than eight months. Cholelithography revealed normal filling of the biliary tree with fine branches. The opaque medium soon was emptied freely into the duodenum.

COMMENT

The symptoms observed in these cases are quite representative of those described in the cases reported in the literature. In many cases they are indistinguishable from the symptoms of cholecystitis. This brings up an interesting thought. The difficulty in judging the pathologic status of the gall bladder from the symptoms in cholecystitis proper has been stressed repeatedly and explained by various theories. Too often, because of the frequent presence of stones in cases of cholecystitis, one tends to accept the simple, easily visualized explanation associating calculous obstruction of the cystic or common bile duct with colic. This path is sometimes misleading and one may encounter, on one hand, a distended hydropic gall bladder after an empyema due to an impacted cystic duct stone in a case in which there is no history of colic, or acute cholecystitis with gangrene and impending perforation and in which the symptoms have largely subsided. On the other hand, in cases in which patients complain of severe colic there may be few findings in the gall bladder and no stones. Without appearing to draw too many conclusions from a rare anomaly, we would like to suggest that the symptoms of cholecystitis may frequently be a reflection of a process going on in the common bile duct or its sphincter rather than in the gall bladder. If this be true, subsidence of symptoms associated with improvement in the common bile duct or its sphincter might occur while the disease in the vesicle can go on to gangrene and perforation. Evaluation of this suggestion would be difficult because of the rarity of the opportunity to get sections of the common bile duct and its sphincter during this stage of cholecystitis.

In four of our cases the patients complained of pain which extended to the left side of the thorax and subscapular region. This is not usual in cases of acute or chronic cholecystitis but has been described from time to time as referred pain in disease of the common bile duct. In none of the cases of congenital absence of the gall bladder has the anomaly been suspected preoperatively as there is no point of distinction from cholelithic disease with a nonfunctioning gall bladder on roentgenologic examination. As competent surgeons easily can overlook an unusually placed gall bladder, failure to find it during

laparotomy is less convincing than is the discovery of this anomaly at necropsy. In order to make certain that the gall bladder is not present, the common bile duct must be identified throughout its entire length. If a T tube is inserted into the common bile duct and if a choledochogram is made, either in the course of or after operation, the possibility of an intrahepatic gall bladder may be eliminated. If the appendix previously has been removed by a sufficiently large incision, there is a possibility that the gall bladder also may have been removed without the knowledge of the patient. A small nubbin at the site of the gall bladder occasionally may be the result of repeated inflammatory episodes.

Interesting speculation is stimulated by the cases reviewed here. Although congenital absence of the gall bladder is rare, the state of the extrahepatic biliary tract is comparable physiologically with the post-cholecystectomy state. It offers, so to speak, a naturally occurring opportunity to study the effect of absence of the gall bladder. In 58 per cent of the cases of congenital absence of the gall bladder reported since 1900, the patients have had symptoms suggestive of cholecystic disease with a slight variation in that the pain occasionally extended to the left subscapular region. Forty-eight per cent of the patients had jaundice. In 27 per cent of the cases there were stones in the common bile duct. If one limits the discussion to cases in which the patients were more than 45 years of age, symptoms were present in 73 per cent of the cases. This high incidence of symptoms in the cases reported suggests the existence of some defect in the dynamics of the biliary tract. Doubt is cast on this by the high incidence of cases in which complete relief follows cholecystectomy. Critical evaluation of the situation reveals some similarity to the clinical picture of so-called postcholecystectomy syndrome. The discussions that have marked this postoperative difficulty are applicable here.²⁷⁻²⁹ The problem brings up theories of the dynamics of the biliary tract, spasm of the sphincter of Oddi, disturbed rhythmic function of the sphincter, the normal intermittence of biliary flow, the effects of pancreatitis and cholangitis, and the "tension bulb effect" of the gall bladder. A mechanical analogy to the last effect may be found in the mouth blowpipe used in chemistry. The skilled operator distends his cheeks as widely as possible while blowing through the tapering tube. This permits a steady flow of air through the pin-point tip of the tube for long periods of time while the operator breathes comfortably. The rhythmic bellowslike action of the lungs keeps the reservoir in the distended cheeks full. It is possible that in this manner the gall bladder acts as a pump reservoir and prevents a sudden fall of pressure in the biliary tract (and in some cases the pancreatic ducts) on opening of the sphincter of Oddi. This would help the sphincteric action in the prevention of regurgitation of the duodenal contents and help to adjust the pressure in the biliary tract to that of the pancreatic ducts when necessary by

changes in the size of the gall bladder. Giordano and Mann^{30, 31} have shown that, in animals which do not have a gall bladder, bile is expressed from the sphincter in an intermittent trickle while in species with a gall bladder the bile is expressed in spurts at the proper stimulus.

To what extent, if any, the common bile duct, hepatic ducts, or intra-hepatic bile ducts take over some of the functions of the gall bladder is a moot point. Cox³² has shown that in rats, which never have a gall bladder, ligation of the common bile duct mechanically produces the changes in the parietal sacculi which generally are accepted as evidence that the hepatic ducts have taken over the function of the gall bladder. In the wall of the duct, which is made up of fibroelastic tissue, there is little muscle. The common bile duct was dilated in nineteen, or 32 per cent, of the sixty cases. In nine of the nineteen cases in which the duct was dilated, stones were present. With the gall bladder absent, it is possible that stasis of the contents of the biliary tract is greater than it is when the gall bladder is present. At any rate, it appears that congenital absence of the gall bladder is a distinct disadvantage. Jaundice was present in 48 per cent of the cases; in 21 per cent of the cases the jaundice was not associated with stones. Stones were present in 27 per cent of the cases, pancreatitis in 18 per cent, and hepatitis in 8 per cent (on gross examination). The clinical picture certainly warrants the assumption that disease of the biliary tract is more common in cases of congenital absence of the gall bladder than it is in cases in which the gall bladder is present, especially in cases in which the patients are 45 or more years of age. Proponents of reflux theories would find fertile soil here. In one case, pancreatitis of the acute hemorrhagic necrotic variety was found.³³ It has been pointed out repeatedly that cholecystitis is a disease of the biliary tract which finds its most prominent manifestation in the gall bladder. The next point of least resistance is the cystic duct, and at times the disease may be found there with a relatively normal fundus.³⁴ In the absence of the gall bladder and cystic duct the remaining portion of the biliary tract will reflect the disease, be it inflammatory, mechanical, metabolic, chemical, or a combination of all. In an attempt to explain the icterus in cases of jaundice without stone, it is interesting to note that pancreatitis was noted in nine of the thirteen cases and hepatitis in three cases.

In anatomic teaching, it usually is implied that the fossae and impressions on the surface of the liver are produced by pressure of the neighboring organs. Although this seems to be a logical conclusion, in seven cases the fossa for the gall bladder was present in the liver despite the fact there apparently was no gall bladder to create the depression.

Although the number of cases has been, of necessity, small, in ten of the twelve cases of congenital absence of the gall bladder in which

the common bile duct was drained for a prolonged period (three of our cases and nine collected from the literature) complete relief of symptoms was obtained. Similar experience has been obtained in the treatment of "postcholecystectomy syndrome."³⁵ In one of our cases (Case 2), a T tube was left in the common bile duct for two years despite the fact that there had been no stones or dilatation of the duct. In the four other cases in which symptoms existed, no drainage was employed and the patients continued to complain of the same symptoms. On the basis of this evidence, we advise prolonged drainage of the common bile duct by means of a T tube in cases of congenital absence of the gall bladder in which symptoms are present, even when the common bile duct is of normal size and stones are not found.

SUMMARY

This paper is based on fifty cases of congenital absence of the gall bladder that have been reported since 1900, and on ten cases that have been observed at the clinic. Symptoms resembling those of cholecystic disease were present in 58 per cent of the sixty cases. Forty-eight per cent of the patients had jaundice and 27 per cent had stones in the common bile duct. Symptoms were present in 73 per cent of the cases in which the patients were more than 45 years of age. Prolonged drainage of the common bile duct with a T tube is advocated in the cases in which symptoms are present.

REFERENCES

1. Latham, Arthur: Absence of the Gall Bladder, *Proc. Anat. Soc. Great Britain & Ireland*, pp. 39-40, 1898.
2. Schachner, August: Anomalies of the Gall-Bladder and Bile-Passages; With the Report of a Double Gall-Bladder and a Floating Gall-Bladder, *Ann. Surg.* 64: 419-433, 1916.
3. Gay, R. J.: Developmental Anomalies of the Gall Bladder With Report of a Case, *Tr. Chicago Path. Soc.* 5: 108-113, 1902.
4. Buddy: Über angeborene Gallenblasenverkümmerng, *Arch. f. klin. Chir.* 126: 45-47, 1923.
5. Theodor, F.: Angeborene Aplasie der Gallenwege verbunden mit Lebercirrhose, durch Operation behandelt, *Arch. f. Kinderh.* 49: 358-366, 1909.
6. Bower, J. O.: Congenital Absence of the Gall-Bladder, *Ann. Surg.* 88: 80-90, 1928.
7. Gross, R. E.: Congenital Anomalies of the Gallbladder, *Arch. Surg.* 32: 131-162, 1936.
8. Danzis, Max: Congenital Absence of the Gall Bladder, *Am. J. Surg.* 29: 202-207, 1935.
9. Fowler, R. H.: Anomalies of the Gall Bladder and Bile Ducts, *Med. Times* 45: 230-232, 1917.
10. Torrance, Gaston: Congenital Absence of the Gall-Bladder; Report of a Case, *Tr. Am. Ass. Obst. & Gynec.* 32: 386-387, 1919.
11. Whipple, A. O.: Surgery of the Biliary Tract; Cases for Postoperative Discussion: I, II, and III; Case for Operation: IV, *S. Clin. North America* 1: 373-389, 1921.
12. Finney, G. G., and Owen, J. K.: The Surgical Aspect of Congenital Absence of the Gall Bladder; Report of Two Cases, *Ann. Surg.* 115: 736-744, 1942.
13. Gordon, W. C., and Dragutsky, D.: Congenital Absence of the Gall Bladder and Cystic Duct; Report of a Case, *J. Lab. & Clin. Med.* 27: 594-597, 1942.
14. Melville, A. G. G.: A Case of Absence of the Gall Bladder and Duodenal Diverticulosis, *Acta radiol.* 18: 65-69, 1937.

15. Robertson, H. F., Robertson, W. E., and Bower, J. O.: Congenital Absence of the Gallbladder; With a Primary Carcinoma of the Common Duct and Carcinoma of the Liver, *J. A. M. A.* 114: 1511-1517, 1940.
16. Sarma, P. J.: The Congenital Absence of Gall Bladder, *Am. J. Digest. Dis.* 8: 139-141, 1941.
17. Tallmadge, G. K.: Congenital Absence of the Gallbladder, *Arch. Path.* 26: 1060-1062, 1938.
18. del Carril, M. J., Veignolle, M. J., and Díaz Bobillo, I.: Ictericia y malformación congénita de vías biliares, *Rev. Asoc. méd. argent.* 49: 145-151, 1935.
19. Mauro, E.: Auscência congênita da vesícula biliar, *Ann. paulist de med. e cir.* 40: 85-90, 1940; (Abstra.) Congenital Absence of the Gall Bladder With Report of a case, *Internat. S. Digest* 30: 319, 1940.
20. Pólya, J.: Rare Case of Lithiasis of Hepatic Bile Ducts in Congenital Absence of Gallbladder, *Orvosi hetil* 79: 715-718, 1935.
21. Keibel, Franz, and Mall, F. P.: *Manual of Human Embryology*, Vol. 2, Philadelphia, 1912, J. B. Lippincott Company, pp. 410-413.
22. Mentzer, S. H.: Anomalous Bile Ducts in Man; Based on a Study of Comparative Anatomy, *J. A. M. A.* 93: 1273-1277, 1929.
23. Mentzer, S. H.: Comparative Anatomy of the Biliary System, *California & West. Med.* 30: 315-321, 1929.
24. Thomson, S. C.: The Extrahepatic Biliary Tract of the Hyrax, *Anat. Rec.* 72: 445-449, 1938.
25. Eschner, A. A.: Congenital Absence of the Gall-Bladder, *Med. News*, Philadelphia 64: 548, 1894.
26. Miller, J. K.: Congenital Absence of the Gall Bladder, *Am. J. Surg.* 33: 315-316, 1936.
27. Walters, Waltman, and Thiessen, N. W.: Visual Methods of Studying the Physiology of the Common Bile Duct. I. The Problem of Pancreatitis and Sphincteritis, *Proc. Staff Meet., Mayo Clin.* 9: 772-775, 1934.
28. Weir, J. F., and Snell, A. M.: Symptoms That Persist After Cholecystectomy; Their Nature and Probable Significance, *J. A. M. A.* 105: 1093-1098, 1935.
29. Hill, H. A.: Functional Disorders of the Extra-Hepatic Biliary System: Biliary Dyssynergia or Dyskinesia, *Radiology* 29: 261-278, 1937.
30. Giordano, A. S., and Mann, F. C.: The Sphincter of the Choledochus, *Arch. Path. & Lab. Med.* 4: 943-957, 1927.
31. Mann, F. C.: A Comparative Study of the Anatomy of the Sphincter at the Duodenal End of the Common Bile-Duct With Special Reference to Species of Animals Without a Gall-Bladder, *Anat. Rec.* 18: 355-360, 1920.
32. Cox, F. W.: Changes in the Bile Ducts and Parietal Sacculi Following Absence of the Gall Bladder, *Surg., Gynec. & Obst.* 55: 168-176, 1932.
33. Siewerth, W. S.: Necrosis of the Pancreas With Congenital Absence of the Gall Bladder, *Illinois M. J.* 63: 327-329, 1933.
34. Gray, H. K., and Sharpe, W. S.: Biliary Dyskinesia; Role Played by Remnant of Cystic Duct, *Arch. Surg.* 46: 564-571, 1943.
35. Judd, E. S.: Condition of Common Duct After Cholecystectomy, *J. A. M. A.* 81: 704-709, 1923.

THE INFLUENCE OF THE LOCAL APPLICATION OF SULFATHIAZOLE ON THE INCIDENCE OF INFECTIONS IN SURGICAL INCISIONS

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NEW forms of sulfonamide drugs with increased bacterial specificity are constantly being developed. Various methods of administration have been used in an attempt to increase their effectiveness. With wound infection still the most common and serious single hazard of surgery, it follows that the surgeon's interest should be directed to the sulfonamide drugs in a quest for the particular form and type of administration best suited to his needs. For this reason it seems only natural that the surgeon's study should turn to the direct application of the sulfonamide drugs to tissues in an attempt to prevent and control infection. Contradictory results and opinions¹⁻³ have been published recently regarding the efficacy of this method. Part of this controversy arises because the authors fail to make clear whether or not they are treating tissues already infected or tissues merely contaminated with bacteria and therefore sites of potential infection. Meleney and his associates³ have published the most recent and exhaustive study yet made in man of the value of the direct application of the sulfonamide drugs to what they termed contaminated wounds. They divided the patients used for controls and those treated with sulfonamides into groups based on the amount of tissue damage and the degree of bacterial contamination present in the wounds at the time of treatment. They concluded from this study that the local application of sulfonamide drugs to contaminated wounds will not reduce the incidence of infection in such wounds. They regarded the wounds being treated as contaminated wounds, but they stated that the cases were divided into two groups, one group in which the wounds were treated within three hours and the other in which they were treated after three hours, from the time of the accident. It would seem that in this latter group some of the wounds would be truly infected wounds, not merely contaminated. It is significant to note that in the discussion of this paper, Lockwood, one of the collaborators, pointed out that their conclusion did not mean that on the battlefield the direct application of the sulfonamide drugs to contaminated but not yet infected wounds was of no value. He believed the sulfonamide drugs should be used on such emergency occasions on the battlefield to prevent the multiplication of organisms while casualties await further treatment.

Received for publication, Sept. 20, 1944.

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This present paper deals with the possibility of preventing wound infections in clean surgical incisions, by the application of sulfonamide drugs to such incisions before there is opportunity for contamination to occur. The clear division of wounds into (1) those in which infection is established, (2) those in which contamination is already present before the sulfonamide drugs are applied, and (3) those in which the contamination occurs after the application of the sulfonamide drugs, should be kept in mind, and results of the treatment of these three groups of wounds should not be confused.

The present study was undertaken because of the frequent and serious infections which develop in the incisions made for lobectomies and pneumonectomies. When a number of such incisions had been treated by the direct application of sulfathiazole before contamination of the incision had occurred, the results appeared of sufficient interest to compare with those following similar incisions not treated with any sulfonamide drug. The only cases available for comparison were an equal number of patients in whom lobectomies or pneumonectomies had been done in the period immediately preceding that in which sulfathiazole was employed. Aside from the application of sulfathiazole to the incisions in the one group there are also some minor differences in the treatment used in these two series of cases which will be discussed fully in their proper place, but these are not of sufficient importance to preclude a comparison of the results in these two groups.

MATERIAL AND METHODS

Seventy incisions for lobectomies* and pneumonectomies† were studied. The incisions in all but one‡ case were curving incisions just below the scapula, approximately over the fifth or sixth interspace, extending from close to the midline posteriorly to just beyond the anterior axillary line anteriorly and measuring from 30 to 35 cm. in length. The incisions passed through the skin and subcutaneous tissue, and posteriorly through the trapezius and rhomboid muscles, anteriorly through the latissimus dorsi and serratus anterior. The control or prior group consisted of thirty-five patients. The age of these patients ranged from 9 to 52 years, the average age being 31. The experimental group consisted of the thirty-five patients operated upon in the period immediately following that in which the control group of patients came to operation. The age of these patients ranged from 11 to 57 years of age, the average being 32. In the incisions of this experimental group *not more than 2 Gm.* of sterilized sulfathiazole powder were rubbed into every nook and cranny of these extensive incisions *before* opening into the pleural cavity, thus producing a film of serum and blood saturated

*Lobectomy refers to the removal of individual lobes.

†Pneumonectomy refers to the removal of a complete lung.

‡A shorter anterior incision was used.

with sulfathiazole overlying all of the exposed tissue. The lung lesions for which lobectomy or pneumonectomy were done in both groups of cases are set forth in Table I. From this table and the preceding para-

TABLE I

FREQUENCY OF INCISIONAL INFECTIONS IN RELATION TO THE LUNG LESIONS FOR WHICH LOBECTOMY AND PNEUMONECTOMY WERE DONE IN BOTH CONTROL AND EXPERIMENTAL GROUPS

LESION	UNTREATED WOUNDS			TREATED WOUNDS		
	NO. OF CASES	NO. OF WOUNDS INFECTED	PER CENT OF WOUNDS INFECTED	NO. OF CASES	NO. OF WOUNDS INFECTED	PER CENT OF WOUNDS INFECTED
Carcinoma	3	1	33.3	4		
Bronchiectasis	15	4	26.7	17	3	17.6
Lung abscess	10	7	70.0	8	1	12.5
Tuberculosis	3	0		3		
Cystic disease	3	1		0		
Hemoptysis	1	0		1		
Bronchial stricture	0	0		1		
Neurogenic sarcoma	0	0		1		
Total	35	13	37.1	35	4	11.5

graph the two series are seen to form closely comparable groups of cases both from the point of view of age and the pulmonary lesions for which the operations were undertaken.

RESULTS

The results of treatment of the wounds with sulfathiazole as compared with treatment omitting the direct application of any sulfonamide compound to the wounds is set forth in Tables I and II, the former

TABLE II

FREQUENCY OF INCISIONAL INFECTION IN TWENTY-FIVE CASES OF LUNG ABSCESS AND BRONCHIECTASIS FROM BOTH THE CONTROL AND EXPERIMENTAL GROUPS

LESION	UNTREATED WOUNDS			TREATED WOUNDS		
	NO. OF CASES	NO. OF WOUNDS INFECTED	PER CENT OF WOUNDS INFECTED	NO. OF CASES	NO. OF WOUNDS INFECTED	PER CENT OF WOUNDS INFECTED
Lung abscess	10	7	70.0	8	1	12.5
Bronchiectasis	15	5	33.3	17	3	17.6
Total	25	12	48.0	25	4	16.0

group being referred to as treated wounds and the latter as untreated wounds. Among the thirty-five cases of the untreated control group, thirteen wound infections occurred, an incidence of 37.1 per cent. It is of importance to note that all of these infections were serious, usually developing a definite abscess and spreading cellulitis of the chest wall requiring either simple opening of the incision or more radical surgical drainage. The organisms from these infected wounds varied from pure cultures of *Streptococcus hemolyticus*, *Staphylococcus aureus*, and *Streptococcus viridans* to the typical mixed flora found in infected

lungs. Eleven of these infections developed between the sixth and tenth days postoperatively, while one occurred twelve days and another seventeen days postoperatively. Twelve of these wound infections developed in cases where operation was carried out for the excision of grossly infected lungs. Four of these latter were cases of bronchiectasis, seven were cases of lung abscess, and one was a case of congenital cystic disease of the lung. The remaining infected wound occurred in a patient with a bronchogenic carcinoma. In nine of these patients with infected wounds, empyemas developed. It is not possible from the available data to determine how often this serious complication was secondary to the infected wound, but in a few of these cases which came under my own observation, it was seen that when a patient who suffered from a wound infection coughed, bubbles of air and pus were forced out of the incision in the expiratory phase and during the inspiratory phase this pus was sucked back into the pleural cavity. In these patients sterile pleural effusions were present before the clinical detection of the infected wounds.

In the thirty-five cases of the treated or experimental group, four wound infections occurred, an incidence of 11.5 per cent. Three of the wound infections were slight. One occurred at the end of six days; culture yielded a pure growth of *Streptococcus hemolyticus* and empyema followed the wound infection. Two of the wound infections occurred three weeks after the operation, at a time when the wounds were apparently well healed. The same peculiar features occurred in both cases. Within the course of a few days the epithelium thinned out, the incision broadened at many points along the wound and finally broke down, producing multiple superficial ulcerations which yielded a culture of *Staphylococcus aureus* in the one case and mixed organisms in the other. Five weeks later there occurred in one of these cases a clinically detectable empyema. The remaining case of wound infection in the experimental series was extensive, characterized by a copious serosanguineous exudate associated with mild infection. Empyema also developed in this patient.

It is interesting to note that in both series the majority of infections developed in cases where operation was performed in the presence of grossly infected lung tissue. This is clearly shown in Table II. In the control group, twelve of the infected wounds occurred in a total of twenty-five cases of bronchiectasis or lung abscess, an incidence of 48 per cent, while in the experimental group in an equal number of similar cases wound infections developed in only four, an incidence of 16 per cent.

DISCUSSION

These results strongly suggest that sulfathiazole powder rubbed carefully into a recent clean operative incision will decrease the incidence and severity of wound infection that might otherwise have developed

from bacterial contamination occurring later in the course of the operation. However, there are some differences in the treatment between the two groups of cases which must be considered before accurate conclusions can be drawn from the results presented in this paper.

Some difference existed in the method of closing the chest, in the two series. In the control series, twenty of the chests were treated by closed drainage* following operation, while the remaining fifteen patients were treated by complete closure† of the chest. This latter method was used in thirty-two cases of the experimental series. It might be felt that this difference in treatment could account for the increased incidence of infection in the wounds of the control group. However, an analysis of the control group shows that five wound infections developed in the fifteen cases in which the chests were completely closed, an incidence of 33.3 per cent, while among the twenty cases treated by closed drainage, wound infection developed in eight, an incidence of 40 per cent. These results appear to indicate that the difference in the method of closing the chest was not an important factor influencing the development of wound infections in these patients.

In the two groups of cases under consideration there was some difference in the technique of removing the lung. In those treated, all the pneumonectomies and all except one of the lobectomies were done by the dissection method. In this method, dissection of individual structures and separate ligation of these structures close to the lung hilus was carried out and the main bronchus of the lobe was cut as far proximally as possible. In the control series, nineteen of the operations were done by this same method but fourteen lobectomies were done by the tourniquet method.‡ Here the lobe to be removed was freed until a tourniquet could be passed about a small pedicle of lung tissue, including its bronchi and blood vessels. The lung was cut distal to the tourniquet, and the pedicle of lung tissue oversewn before the tourniquet was released. In all patient where a lobectomy was done by the tourniquet method, closed drainage of the pleural cavity was carried out. A good deal of unavoidable bacterial contamination of the pleural cavity and wound must result during removal of lung tissue by the tourniquet method. However, the incidence of wound infection in the fourteen cases in which the tourniquet method was employed in the control series was only 28.5 per cent. This is less than the incidence of infected incisions in the total control group.

It is also interesting to note that in the control series there are fifteen cases in which the dissection technique of removal of the lung and complete closure of the chest were done. These fifteen cases compare identically in these respects with thirty-four cases of the experimental

*Refers to an airtight fitting tube in'o the pleural cavity with the other end under fluid below the bed level.

†Refers to complete closure of the operative incision with no provision made for draining the pleural cavity.

‡All of these chests were drained.

group. Among these fifteen cases in the control group the incidence of wound infection was 33.3 per cent as compared to an incidence of 11.5 per cent in the experimental group.

The development of wound infection must depend largely on the degree of contamination of these incisions, which in turn depends to a great extent on the infection in the lung. The most severely infected lungs are those of bronchiectasis, lung abscesses, and congenital cystic disease of the lung. In the prior group all but one of the wound infections occurred in cases of lung abscess or bronchiectasis, while in the experimental group all of the wound infections occurred in similar cases. In the untreated group there were seven wound infections in ten cases of lung abscess, and five wound infections in fifteen cases of bronchiectasis. In the experimental series, there was one wound infection in eight cases of lung abscess, and three wound infections in seventeen cases of bronchiectasis. These figures are shown well in Table II and it is significant to note that in the group of cases of lung abscess or bronchiectasis in the control series, the incidence of wound infection in twenty-five cases is 48 per cent, while in an equal number of similar cases in the experimental groups the incidence of wound infections is only 16 per cent. However, the greatest difference in the incidence of wound infection is among the cases of lung abscess where 70 per cent of the wounds were infected in the control group and only 17 per cent in the experimental group. In these cases of lung abscess, aside from the local application of sulfathiazole in the experimental group, no difference in the operative technique existed between the two groups which might account for this great difference in the incidence of wound infection.

The method of the general administration of sulfonamide drugs differed between the two groups of patients studied. In the control series, sulfonamide drugs when administered, were most often given within twenty-four to forty-eight hours after operation and by mouth, while in the experimental group all but nine of the patients received sulfathiazole intravenously on the day of operation. Six of the wound infections developing in the control series were in patients who received some sulfonamide compound by mouth within twenty-four hours after operation, while the four wound infections occurring in the experimental series occurred in patients who received sulfathiazole intravenously on the day of operation.

Blood loss was treated in both groups of patients by transfusions of adequate amounts of whole blood during and after operation. While some details of postoperative care varied from time to time, there were no significant differences in this respect between the control and experimental group. It is scarcely possible to consider variation of general resistance to infection among the different patients.

From this analysis it appears that the only factor influencing the different incidence of wound infection in the two groups of incisions

compared in this study was the careful application to the wounds in the experimental group of sterilized sulfathiazole powder before opening into the pleural cavity. In order to determine if the different incidence of wound infection in these two groups could arise merely from chance difference, the figures from the two groups of cases were subjected to a statistical analysis according to accepted statistical methods as described by Hill⁴ and Campbell.⁵ This analysis demonstrated that the differences in the results between the experimental and control groups and the differences between the subdivisions of groups of cases of bronchiectasis and lung abscess were all statistically significant.

In view of the mixed flora present in infected lungs, the local application of sulfathiazole in the prevention of wound infections in the experimental group would seem to indicate activity against a wide variety of organisms. In vivo and in vitro studies point to the fact that the bacteriostatic effect of the sulfonamide drugs is against a large number of organisms.^{6, 7} Possibly many of the wound infections that develop in cases of this type are of a symbiotic nature, and bacteriostatic action against one type of organism is all that is necessary to prevent the development of infection.

Regardless of the exact mode of action of the sulfonamide drugs, the patient's own defenses play the final rôle in the prevention of wound infection. Suppression by the sulfathiazole of the activity and multiplication of bacteria prevents rapid destruction of the patient's tissues and allows the individual's general antibacterial and local inflammatory defenses to come into action before active and definite infection has occurred. It would appear that this well-developed local inflammatory response would be much more effective in destroying a few bacteria present in the wound, than could be possible if infection were well established and causing destruction of tissues before the inflammatory reaction had reached its height.

A study of two of the wound infections in the experimental group is most enlightening in an attempt to understand the effect of sulfathiazole as used in this group of patients. Both wounds were apparently well healed and completely epithelized. Three weeks after operation there was a slow widening of the incision at many points, finally resulting in multiple superficial ulcerations. In one case the organisms cultured were *Staphylococcus aureus* and in the other a mixed flora was found. It was apparent that organisms lying throughout the whole length of these wounds had remained relatively dormant for three weeks. Then, due to unknown factors, their relative virulence increased to a point where they were able to produce active infection. *In spite of this apparent masking of wound infection it is important to point out that these infections were slight compared to any of the wound infections that developed in the control series and especially insignificant compared to some of the large abscesses occurring in the control series.* It also seems worthy of note that these infections occurred at a time

when the deeper structures would be well healed, and therefore penetration into the pleural cavities would not be as likely to occur as in the infections occurring in the control group around the sixth to eighth day after operation.

Numerous objections have been raised to the local application of sulfathiazole to wounds. One of these objections is that it delays healing. This seems unimportant, if its use prevents the mortality and morbidity arising from wound infection. In the experimental group, the sutures were removed between the sixth and eighth day and all except one of the wounds appeared well healed. Others suggest that all of the advantages of the direct application of sulfathiazole can be accomplished by the intravenous use of the drug but this is not substantiated in the present study. Moreover, while idiosyncrasies and sensitivities to the sulfonamide drugs do occur,¹² serious reactions are encountered more often when these drugs are given by mouth or intravenously. In patients who are sensitive to the sulfonamides, the local application of these drugs may result in a local reaction of hyperemia, serous exudation, and delayed healing, and may well form the basis for one of the infections in the experimental group which showed only mild infection but a copious serous exudate. The recent intradermal test for sensitivity to the sulfonamide drugs developed by Leftwich¹³ could be used preoperatively to exclude such individuals in whom the local use of sulfathiazole would be contraindicated. In spite of these objections the logic of the local use of sulfathiazole over other methods of administration for the prevention of wound infections under the conditions in this study is apparent when we consider that the direct application of sulfathiazole accomplishes the maximum concentration of the drug at the most effective place and at the optimum time, with a minimum dose.

It should be stated here that the use of sulfathiazole as carried out in the experimental group is no substitute for careful surgery. However, in spite of all precautions some operative procedures cannot be done without producing some contamination of the incision.

All of the facts presented suggest that sulfathiazole applied to recent sterile operative incisions tends to decrease the severity and reduce the incidence of infection which might otherwise be expected to occur in such wounds as a result of subsequent unavoidable bacterial contamination. Ever since Lister's attempt to produce antiseptic surgical technique, surgeons have continuously sought for a technique to prevent organisms from getting into wounds and establishing infection. The evidence in this paper indicates that the method described accomplishes this to a large degree in certain types of wounds by destruction of contaminating organisms before infection occurs. The facts also suggest the principle that bacteriostatic drugs applied to a wound surface allow the natural defenses of the body to destroy organisms more effectively than these drugs can aid the body in the resolution of an already estab-

lished infection. In order to obtain a true estimate of the value of the local use of sulfathiazole in such operative incisions, further carefully controlled trials of this method of the use of sulfathiazole should be made on a series of alternate patients in whom the operative incisions are subject to unavoidable subsequent contamination. Some situations in which the method might be tried to good advantage are incisions for perforated appendix, perforated peptic ulcer, peritonitis of any origin, empyema, and drainage of a pyonephrosis. Certainly the favorable results reported in this study provide ample justification for further investigation of the method described, and as penicillin becomes available for civilian use, studies along these lines with this new drug may prove fruitful.

SUMMARY

1. Wound infections occurring in thirty-five thoracic incisions for lobectomy and pneumonectomy treated by applying sulfathiazole to the wound before opening the pleura were studied and compared with wound infections in an equal number of similar incision not treated by the local use of sulfathiazole.

2. Thirteen wound infections, an incidence of 37.1 per cent, occurred in the control group, while only four occurred in the experimental group, an incidence of 11.5 per cent. This difference was shown to be statistically significant.

3. All except one of the wound infections in the control group were in cases of bronchiectasis or lung abscess with an incidence of wound infection in these cases of 48 per cent, while in the experimental group all of the wound infections were in cases of lung abscess or bronchiectasis with an incidence of wound infection in these cases of only 16 per cent.

4. After a discussion of other factors which might have accounted for this difference in the frequency of wound infections in these two groups of cases, it was concluded that sulfathiazole applied locally in the experimental series was the only important factor to which the reduced incidence of wound infection in the experimental group could be attributed.

5. Since the publication of Meleney's work³ there has been a fairly widespread feeling that the topical application of sulfathiazole has no place in surgery. The conditions under which his study was made were entirely different from those of the present study and it seems important that the local use of sulfathiazole should not be abandoned under all circumstances without first considering each situation on its own merits. In consideration of these facts and the favorable results of the present investigation it is suggested that further carefully controlled trials of the use of sulfathiazole by the method described in this paper should be carried out.

I wish to acknowledge the kindness of Dr. W. E. Gallie for permission to use the case records from the Surgical Service of the Toronto General Hospital from which this study was made.

REFERENCES

1. Hawking, Frank, and Hunt, Allan H.: Sulphathiazole Used Locally, *Brit. M. J.*, 2: 604-606, 1942.
2. Green, H. N., and Parkin, T.: Local Treatment of Infected Wounds With Sulphathiazole, *Lancet* 205-210, 1942.
3. Meloney, Frank L.: The Study of the Prevention of Infection in Contaminated Accidental Wounds, Compound Fractures and Burns, *Ann. Surg.* 118: 171-192, 1943.
4. Hill, Bradford: Principles of Medical Statistics, Ed. 3, London, 1943, The Lancet Limited.
5. Campbell, Horace E.: The Statistical Method, *Surgery* 9: 825-831, 1941.
6. Green, H. N., and Beischowsky, F.: The Mode of Action of Sulphonamide: II. The Antisulphanilamide and Other Anti-Bacteriostatic Factors in Bacterial Extracts, *Brit. J. Exper. Path.* 23: 1, 1942; III. The Relation of Chemical Structure to the Bacteriostatic Action of Aromatic Sulphur, Selenium and Tellurium Compounds, *ibid.* 23: 13, 1942.
7. Orgain, Edward S., and Poston, Mary A.: Sulphonamide Compounds in Therapy of Bacterial Endocarditis, *Arch. Int. Med.* 70: 777-784, 1942.
8. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following the Clinical and Experimental Use of Sulphonamide Drugs, *Am. J. Path.* 28: 109-121, 1942.
9. Kalz, F., and Steeves, L. C.: Hypersensitivity to Sulphonamides, *J. Allergy* 14: 79-81, 1942.
10. Rich, A. R.: Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarteritis Nodosa, *Bull. Johns Hopkins Hosp.* 71: 375-379, 1942.
11. Simon, M. A.: Pathologic Lesions Following the Administration of Sulphonamide Drugs, *Am. J. M. Sc.* 205: 139-154, 1943.
12. Simon, M. A., and Kaufman, M.: Death Following Sulphathiazole Therapy, *Canad. M. A. J.* 48: 23-27, 1943.
13. Leftwich, William B.: An Intradermal Test for the Recognition of Hypersensitivity to Sulphonamide Drugs, *Bull. Johns Hopkins Hosp.* 72: 26-48, 1944.

APPENDICITIS AND THE SULFONAMIDE DRUGS

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THE local and the systemic use of the sulfonamide drugs in acute appendicitis has changed the attitude of many surgeons toward several phases of the operative management.

"Where there is pus, drain," "In case of doubt, drain," "The worse they smell, the sooner they're well," and other slogans have been, until recently, potent enough to neutralize any given number of arguments to the contrary. Although well-controlled experimental work and clinical observations for years have established the fact that drains drain only a few hours, and are virtually useless in as diffuse a thing as generalized peritonitis, they are still widely used. The operator who has been confronted previously by pelvic and subphrenic abscesses understandably leans toward any procedure that may forestall their occurrence. Certainly it *seems* good sense to leave a route of egress for any noxious material.

It is significant, then, that in dealing with perforated appendices surgeons, with no qualms, are now closing wounds without drainage. Their readiness to dispense now with drainage will probably still be gratifying to the exponents of the nondrainage technique who have spoken forcefully toward this end for some years with but few converts.

Similarly, but less important, are the changes of attitude regarding the use of silk or cotton suture material in contrast to the more popular catgut. It has become apparent that the use of the less irritating silk or cotton will reduce the number of wound infections while giving a stronger closure. With the advent of the sulfonamide drugs used in the operative field, a few surgeons have been encouraged to use these materials to achieve such benefits.

Inasmuch as the source of this report is a collection of cases from a clinic in which the "no-drainage" and silk techniques have been used extensively, especially prior to the sulfonamide era, by a number of operators, we hope to show just what advantages they afford. In contrast to these studies and as a control, there are the cases of surgeons who during the last eight years uniformly used drains in all instances of peritoneal contamination, and performed the suturing with catgut.

To pick up the thread of the story and to see how these observations developed, we go back about eight years to 1936. In brief, before this time, the appendix was removed through a McBurney incision, catgut

Received for publication, June 19, 1944.

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suture material was used, and the abdomen drained "if necessary." "If necessary" meant if there was either peritoneal contamination or pus evident.

Beginning largely at this time, several surgeons adopted the "no-drainage" technique. The record of their experiences, in the succeeding five years, in (A) simple acute appendicitis, (B) gangrenous appendicitis, and (C) perforated appendices with peritonitis will be discussed in the following paragraphs. All of the cases in this study represent an acute inflammatory process. No instances of subacute, interval, or chronic appendicitis are included.

TABLE I

SURVEY OF 650 CASES OF ACUTE APPENDICITIS WITHOUT GROSS CONTAMINATION OF THE PERITONEAL CAVITY

	NUMBER	SUBSEQUENT WOUND INFECTIONS (%)
No drainage	616	5
Subcutaneous drainage	52	43
Intraperitoneal drainage	12	58

A. SIMPLE ACUTE APPENDICITIS

Certainly it appears that drainage often predisposes to wound infection. The great disparity here suggests that the collection of serum about the folds of the drain provides a medium for the proliferation of bacteria, whereas tight closure may circumvent this.

Subcutaneous Drainage.—The idea of drainage of the subcutaneous tissues alone springs from the hope of minimizing wound infections, but there was very little change in their extent as compared with the undrained ones. The total time elapsing from the time of operation until the cessation of drainage showed that those receiving primary subcutaneous drainage took, as a rule, several days less to heal finally. On the other hand there were many more of them.

Intraperitoneal Drainage.—At the present there is no common usage of intraperitoneal drainage for simple acute appendicitis. It will be enough, then, simply to point out the increased number of wound infections which followed.

As a whole, Table I reflects what a majority of surgeons have gathered from their own experience, particularly regarding wound infections.

B. GANGRENOUS APPENDICITIS

Gangrenous appendicitis (without perforation) has been separated from simple acute appendicitis in this study for one reason. It has been evident for some time that gangrene of the appendix is associated with heavier bacterial extravasation into the free peritoneal cavity than if gangrene were not present. Thus it should reasonably be expected that more infectious complications would result.

Actually there were positive cultures of the peritoneal fluid at the time of operation in 88 per cent of the gangrenous wounds as contrasted

TABLE II

DATA ON 100 CASES OF GANGRENOUS APPENDICITIS WITHOUT GROSS PERFORATION OR CONTAMINATION OF THE PERITONEUM

	NUMBER	SUBSEQUENT WOUND INFECTIONS (%)
No drainage	70	29
Subcutaneous drainage	25	72
Intraperitoneal drainage	5	100

with 38 per cent in the simple acute type shown in Table I. As a result of this increase in the presence of bacteria, there were 29 per cent wound infections in the group in which drainage was not done, and 72 per cent wound infections in the ones drained subcutaneously. In addition to these wound infections there were three pelvic abscesses, two of which required drainage. One of these two had been drained intraperitoneally and into the pelvis—certainly a suggestion of the inadequacy of drains in preventing deep intra-abdominal abscesses.

Thus far then, we have demonstrated the ability of the peritoneum to resist purely bacterial contamination as well as the distinctly inferior resistance of the abdominal wall tissues. In the latter the infection localizes usually in the poorly vascularized subcutaneous fat while the deeper muscles, with relatively richer blood supply, are less apt to be involved.

C. PERFORATED APPENDICES WITH PERITONITIS

In the case of perforated appendices where there is not only massive bacterial contamination but also varying amounts of particulate matter from within the gut, the resistance of the peritoneum to infection is severely taxed and that of the abdominal wall tissues is usually overwhelmed.

TABLE III

DATA ON 155 CASES OF ACUTE APPENDICITIS WITH PERFORATION AND GROSS CONTAMINATION OF THE PERITONEUM (1936-1941)

	NUMBER	WOUND INFECTION ONLY (%)	% INTRA-ABDOMINAL ABSCESSSES (PELVIC AND SUBPHRENIC ABSCESSSES, PERSISTENT PERITONITIS)	FATALITIES
No drainage	51	49	28	11.8
Subcutaneous drainage	44	52	32	13.6
Intraperitoneal drainage	60	40	57	23.3

While simple wound infections were quite common in this group, the great difference lies in the type and severity of the infectious sequelae. This is again reflected in the fatality rate of this period (1936 to 1941).

Persistent Peritonitis.—Those patients who had signs of peritonitis (persistent fever, rigid abdomen, no peristalsis) for as much as forty-eight hours after operation are listed in Table IV.

TABLE IV

	NUMBER	PERSISTENT PERITONITIS (%)
No drainage	51	12
Subcutaneous drainage	44	14
Intraperitoneal drainage	60	28

Pelvic Abscesses.—Those developing pelvic abscesses again suggested the failure of drains to really drain. At this time (before the sulfonamide era) evidently an abscess would develop in the pelvis often regardless of whether or not a drain had been inserted there. On several occasions, at subsequent operation, the drain would seem to be satisfactorily draining one pocket, but another near by would have no connection with it.

TABLE V

	NUMBER	PELVIC ABSCESS (%)
No drainage	51	14
Subcutaneous drainage	44	18
Intraperitoneal drainage	60	20

Intestinal Obstruction.—In contrast to the paralytic ileus accompanying peritonitis, mechanical intestinal obstruction occurred occasionally.

TABLE VI

	NUMBER	INTESTINAL OBSTRUCTION (%)
No drainage	51	2
Subcutaneous drainage	44	4.5
Intraperitoneal drainage	60	10.0

As a complicating factor, intestinal obstruction of the mechanical type (usually due in these cases to a kinked loop or adhesions) added greatly to the mortality. It usually appeared from four to ten days after operation. In contradistinction to the ileus of peritonitis there was not a sustained fever, and most important, we feel, there was prominent and persistent hyperperistalsis accompanying the distention. Levin tubes for gastric and duodenal suction often availed but little and at this time (up until 1940) we had not used the Miller-Abbot type of tube.

SILK AND CATGUT

Prior to 1939, catgut was used practically exclusively in all cases of appendicitis. At this time several surgeons began using silk suture material throughout, but limiting the practice to cases of simple acute appendicitis. There was no other change in technique. The results, as compared with the previous 639 cases in which catgut was used, are tabulated in Table VII.

These were not selected cases. We feel that the increased number of wound infections with catgut may be laid to the disintegrating catgut serving as a nidus about which bacteria can proliferate, whereas this reaction about silk may be minimal.

TABLE VII

THE USE OF SILK AND CATGUT SUTURE MATERIAL THROUGHOUT IN ACUTE APPENDICITIS WITHOUT PERFORATION

	NO. OF CASES	WOUND INFECTIONS	PER CENT
Silk	41	1	2.4
Catgut	639	62	9.7

Our original purpose was to extend the use of silk, nylon, and cotton to contaminated wounds and, actually, this was done. However, at this juncture the local use of the sulfonamide drugs came into prominence so the last step in the changing technique reflects both the use of silk suture material and the sulfonamides.

Technique.—Let us recapitulate for a moment on the technique which had thus evolved by 1942. McBurney incisions, no drainage, the use of silk (or nylon or cotton) suture material, and the use of the sulfonamide drugs were fairly well established. To what extent all of the operators adhered to these methods in the next 300 consecutive cases is shown here:

McBurney incisions used in 100 per cent of the cases

Silk suture material used in 96 per cent of the cases

No drainage used in 99.3 per cent of the cases

Sulfonamides used intraperitoneally and in the wound in 97 per cent of the contaminated (perforated) cases; in simple acute appendicitis it was used at the operator's discretion

The results in the last 300 cases have been more than gratifying, first in the remarkably low mortality, and second in the paucity of infectious complications. The entire story is told in Table VIII.

TABLE VIII

RESULTS OF THE LAST 300 CASES OF ACUTE APPENDICITIS

	CASES	INFECTIOUS COMPLICATIONS	DEATHS
Acute	232	2 wound infections	0
Gangrenous	31	1 wound infection	0
Perforated		11 wound infections	
appendices	33	2 pelvic abscesses	1
		1 subphrenic abscess	
Abscesses	4 (drainage, catgut)	4 wound infections	0
Overall mortality			0.3%

Several features of this type of management require some further elaboration.

1. *Wound Infections.*—Wound infections were unusual, and those that occurred did not persist unduly even with silk in the wound. Despite the presence of infection about the appendix at the time of operation, the vast majority heal with no difficulty at all. Those that became infected drained, as near as we could judge, about 50 per cent

longer than the average catgut wound. In our opinion this is a small price to pay for the large number of totally uninfected wounds.

On the other hand, we are offering no statistics on wounds in which *catgut* and the sulfonamide drugs were used, as there were comparatively few of these. Despite the protracted argument over the merits of catgut and of silk, we doubt very much if any life has ever been lost or any great harm done from the use of one suture material over the other. We are here simply emphasizing our own experience with the nonabsorbable sutures which, both before and since the general use of the sulfonamides, have reduced the number of wound infections.

2. *Pelvic Abscesses*.—Of the last 300 cases only two pelvic abscesses were drained. This statement perhaps does not represent the true situation in that at least seven other wounds showed an inflammatory process going on in the pelvis which resorbed with no other therapy than continued administration of the sulfonamide drugs (usually sulfadiazine) by mouth. These pelvic inflammations appeared from the third until the tenth day, and were accompanied by moderate fever, pulse elevation, and leucocytosis. There was a boggy mass palpable per rectum and, somewhat less frequently, tenesmus. However, none was drained, nor was there recurrence of the mass in any.

COMMENT

While this communication was intended to deal mainly with the changes in technique during the last few years, it is only fair to mention one other factor which is also affecting the present picture. This is the obviously earlier diagnosis and operation in appendicitis.

TABLE IX

	PER CENT IN 1934	PER CENT IN 1938	PER CENT IN 1942
Acute	59	71	76
Gangrenous	10	8	10
Perforated	21	16	12
Abscess	10	5	2

The shift away from patients with appendiceal abscess and peritonitis, and the increase in the simple acute cases need no further elaboration.

SUMMARY

1. A lessening of wound infection and an apparent lowering of mortality were attained when all forms of drainage of the peritoneum and abdominal wall were relinquished. There was no perceptible increase or decrease in the number of intra-abdominal abscesses or in generalized peritonitis.

2. The use of silk suture material reduced the number of wound infections appreciably. Those wounds which *were* infected drained approximately 50 per cent longer than the usual wound in which catgut was used.

3. The use of the sulfonamide drugs locally, used in conjunction with silk suture material and no drainage, has shown remarkable benefits in:

- a. Lowering the mortality still further
- b. Lessening wound infections
- c. Reducing severity of wound infections
- d. Lessening the number and severity of intra-abdominal abscesses

4. The use of the sulfonamide drugs and the no-drainage technique has already been accorded general acceptance. The chief purpose of this paper is to accentuate this. The choice of suture material is a factor which plays a lesser role. Our preference is the nonabsorbable suture material, for with it there seems to be a decided lessening of wound infections.

THE PREVENTION OF STAPHYLOCOCCUS INFECTIONS OF THE PERITONEUM

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METHODS of study of infections in animals always entail great difficulty in the control of many factors which influence the course of the infection. Control of the virulence of the organism is only one of the factors which has to do with the creation of infections which are similar in different animals. In studies of the effects of the sulfonamides by many investigators, these variable factors have been controlled in part by the use of large numbers of small animals. Mice are usually used and in most studies microorganisms have been administered intravenously and the various drugs given by mouth. By varying the number of organisms injected and the dose of drug used, the comparative efficacy of the drugs can be assayed with a fair degree of accuracy.

An evaluation of the effect of bacteriostatic agents which are implanted in contaminated wounds is even more difficult. Organisms introduced into wounds of the skin and subcutaneous tissues, or introduced through a needle into the subcutaneous tissues, give rise to widely varying lesions in different animals. This is true even when frozen *Staphylococcus aureus* is used, and in our experience the virulence of this organism, frozen at $-78^{\circ}\text{C}.$, has remained remarkably stable over long periods of time. The effect of the addition of the sulfonamides to such contaminated wounds has, in our hands, been impossible to interpret with exactness. The measurement of the tension required to separate wound edges is of value in the study of the rate of healing of wounds created under exacting "aseptic" conditions. When the many variable factors which influence infections and those concerned with the bacteriostatic effects of the sulfonamides upon bacteria are introduced, the results obtained from such experimental studies as these again become extremely confusing.

It seemed to us that by creating generalized infections of the serous cavities of animals, which were lethal in most instances, the efficacy of various bacteriostatic agents when used locally could be studied to advantage. In a recent publication¹ we reported experiments which tested the local effect of sulfanilamide, sulfathiazole, and sulfadiazine upon the prevention of infection of the pleural cavities of dogs fol-

The sulfadiazine used in this work was supplied by Lederle Laboratories, Inc., New York and E. R. Squibb & Sons, New York.

Received for publication, June 19, 1944.

The sulfanilamide and sulfathiazole used in this work were supplied by E. R. Squibb & Sons, New York.

TABLE II

SELENIUM DIOXIDE (0.1 Gm. FROZEN SALINE STAPHYLOCOCCI OF HEMOLYTIC STAPHYLOCOCCI AERIS AND 0.3 Gm. STAPHYLOCOCCI OF PERITONEUM)

Body Weight

EXP.	NO.	DATE AFTER OPERATION (DAYS)	FINDINGS AT AUTOPSY, CASES OF DEATH		CLIMATE OF PERITONEUM AT AUTOPSY
			PERITONEUM	PERITONEUM	
A. Sulfamid- amide 0.3 gm. per kilogram body weight intraperi- toneally	26	1	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	27	2	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	28		Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	29	21	Generalized peritonitis; no adhesions	Generalized peritonitis; many fibrous adhesions	II. Staph. aureus
	30		Sacrificed 11 weeks; no evidence of infection; adhesions +	Sacrificed 11 weeks; no evidence of infection; adhesions +	Sterile
	31		Sacrificed 11 weeks; no evidence of infection; no adhesions	Sacrificed 11 weeks; no evidence of infection; no adhesions	Sterile
	32	2	Generalized peritonitis no adhesions	Generalized peritonitis no adhesions	II. Staph. aureus
	33		Sacrificed 5 weeks; no evidence of infection; adhesions +	Sacrificed 5 weeks; no evidence of infection; adhesions +	Sterile
	34	1	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	35	3	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
B. Sulfamid- amide 0.3 gm. per kilogram body weight intraperi- toneally and 0.5 gm. by mouth every eight hours	36	1	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	37		Sacrificed 9 weeks; no evidence of infection; adhesions +	Sacrificed 9 weeks; no evidence of infection; adhesions +	Sterile
	38		Sacrificed 9 weeks; no evidence of infection; no adhesions	Sacrificed 9 weeks; no evidence of infection; no adhesions	Sterile
	39		Sacrificed 7 weeks; no evidence of infection; no adhesions	Sacrificed 7 weeks; no evidence of infection; no adhesions	Sterile
	40		Pneumonia 4 to 5 weeks; no adhesions	Pneumonia 4 to 5 weeks; no adhesions	Sterile
	41	1.5	Generalized peritonitis no adhesions	Generalized peritonitis no adhesions	II. Staph. aureus
	42		Sacrificed 11 weeks; no evidence of infection; adhesions +	Sacrificed 11 weeks; no evidence of infection; adhesions +	II. Staph. aureus
	43	4.5	Generalized peritonitis evidence of infection; no adhesions	Generalized peritonitis evidence of infection; no adhesions	II. Staph. aureus
	44		Sacrificed 11 weeks; no evidence of infection; adhesions +	Sacrificed 11 weeks; no evidence of infection; adhesions +	Sterile
	45		Sacrificed 11 weeks; no evidence of infection; adhesions +	Sacrificed 11 weeks; no evidence of infection; adhesions +	Sterile

administered. A high paramedian incision was made through the abdominal wall. The omentum and spleen were delivered through the incision. The gastrocolic omentum was divided between ligatures near its attachment to the stomach and colon. It was left attached to the splenic capsule and a ligature of silk was tightly applied at that site. The omentum was in this way completely deprived of its blood supply. A suspension of hemolytic *Staphylococcus aureus*, 0.1 c.c., in normal saline solution was then injected among the loops of intestine. When a drug was introduced immediately after the organism was injected, the peritoneum was replaced. The peritoneum was closed with a continuous silk suture, the fascia and subcutaneous tissues with interrupted

TABLE II

SULFANILAMIDE GROUP: 0.1 C.C. FROZEN SALINE SUSPENSION OF HEMOLYTIC STAPHYLOCOCCUS AUREUS AND 0.5 GM. SULFANILAMIDE PER KILOGRAM BODY WEIGHT

	EXP. NO.	DURATION OF LIFE AFTER OPERATION (DAYS)	FINDINGS AT AUTOPSY, CAUSE OF DEATH	CULTURE OF PERITONEUM AT AUTOPSY
A. Sulfanilamide 0.3 Gm. per kilogram body weight intraperitoneally	26	4	Generalized peritonitis	H. Staph. aureus
	27	2	Generalized peritonitis	H. Staph. aureus
	28		Sacrificed 19 weeks; no evidence of infection, no adhesions	Sterile
	29	21	Generalized peritonitis, many fibrinous adhesions	H. Staph. aureus
	30		Sacrificed 11 weeks; no evidence of infection, adhesions +	Sterile
	31		Sacrificed 14 weeks; no evidence of infection, no adhesions	Sterile
	32	2	Generalized peritonitis	H. Staph. aureus
	33		Sacrificed 5 weeks; no evidence of infection, adhesions +	Sterile
	34	1	Generalized peritonitis	H. Staph. aureus
	35	3	Generalized peritonitis	H. Staph. aureus
	36	4	Generalized peritonitis	H. Staph. aureus
B. Sulfanilamide 0.3 Gm. per kilogram body weight intraperitoneally and 0.5 Gm. by mouth every eight hours	37		Sacrificed 9 weeks; no evidence of infection, adhesions +	Sterile
	38		Sacrificed 9 weeks; no evidence of infection, no adhesions	Sterile
	39		Sacrificed 7 weeks; no evidence of infection, no adhesions	Sterile
	40		Pneumonia 4 to 5 weeks; no evidence of peritonitis, no adhesions	Sterile
	41	1.5	Generalized peritonitis	H. Staph. aureus
	42		Sacrificed 11 weeks; no evidence of infection, adhesions +	Sterile
	43	4.5	Generalized peritonitis	H. Staph. aureus
	44		Sacrificed 11 weeks; no evidence of infection, no adhesions	Sterile

was administered. A high paramedian incision was made through the abdominal wall. The omentum and spleen were delivered through the wound. The gastrocolic omentum was divided between ligatures near its attachments to the stomach and colon. It was left attached to the splenic pedicle and a ligature of silk was tightly applied at that site. The omentum was in this way completely deprived of its blood supply. A suspension of hemolytic *Staphylococcus aureus*, 0.1 c.c., in normal saline solution was then injected among the loops of intestine. When a drug was used it was introduced immediately after the organism was injected. The omentum was replaced. The peritoneum was closed with a continuous fine silk suture, the fascia and subcutaneous tissues with interrupted

TABLE IV
STAPHYLOCOCCUS STRAINS AND 0.3 GM. SULFADIAZINE PER KILOGRAM
BODY WEIGHT

EXPERIMENTAL GROUP	NO. OF ANIMALS	DURATION OF INFECTION (DAYS)	FINDINGS AT AUTOPSY, 24 HOURS AFTER DEATH	CULTURE OF PLUMBERY
A. Sulfadiazine	66	11	Generalized peritonitis	II. Staph. aureus
	67	1.5	Generalized peritonitis	II. Staph. aureus
	68		Sacrificed 3 weeks; no evidence of infection; adhesions +	Sterile
	69		Sacrificed 3 weeks; no evidence of infection; adhesions +	Sterile
	70		Sacrificed 10 weeks; no evidence of infection; adhesions +	Sterile
	71	2	Generalized peritonitis	II. Staph. aureus
	72	2.5	Generalized peritonitis	II. Staph. aureus
	73		Sacrificed 4 weeks; abscess of left upper quadrant; no peritonitis	Sterile
	74		Sacrificed 5 weeks; subphrenic abscess; no peritonitis; adhesions + + +	Sterile
	75		Sacrificed 5 weeks; no evidence of infection; adhesions + + +	Sterile
	76	1	Generalized peritonitis	II. Staph. aureus
	77	1.5	Generalized peritonitis	II. Staph. aureus
B. Sulfadiazine 0.3 Gm. per kilo-gram body weight in trapezioidally and 0.5 Gm. by mouth every 12 hours	80	8	Generalized peritonitis	II. Staph. aureus
	81	2	Generalized peritonitis	II. Staph. aureus
	82	1	Generalized peritonitis	II. Staph. aureus
	83	2	Generalized peritonitis	II. Staph. aureus
	84	2	Generalized peritonitis	II. Staph. aureus
	85		Sacrificed 8 weeks; no evidence of infection; adhesions + + +	Sterile
	86		Sacrificed 5 weeks; subphrenic abscess; no peritonitis; adhesions + + +	Sterile
	87	1	Generalized peritonitis	II. Staph. aureus
	88	1.5	Generalized peritonitis	II. Staph. aureus
	89		Sacrificed 4 weeks; no evidence of infection; no adhesions	Sterile

drug was used in the control experiments. In the other three groups, sulfanilamide, sulfathiazole, and sulfadiazine, respectively were employed. In each experiment 0.3 Gm. of the drug per kilogram of body weight of the animal was the amount used. Coarse crystals of the drug were suspended in about 50 c.c. of sterile distilled water and poured among the loops of small intestine.

About one-half of the animals in each of the groups receiving sulfonamide therapy were also given the drug by mouth, in doses shown in

TABLE I
CONTROL GROUP: 0.1 C.C. FROZEN SALINE SUSPENSION OF HEMOLYTIC
STAPHYLOCOCCUS AUREUS INJECTED

EXP. NO.	PERIATION OF LIFE (DAYS)	FINDINGS OF AUTOPSY CAUSE OF DEATH	CURTURE OF PERI- TONEUM AT AUTOPSY
1	2.5	Generalized peritonitis	II. Staph. aureus
2	4.5	Generalized peritonitis	II. Staph. aureus
3	2.5	Generalized peritonitis	II. Staph. aureus
4	3	Generalized peritonitis	II. Staph. aureus
5	3.5	Generalized peritonitis	II. Staph. aureus
6	6	Generalized peritonitis	II. Staph. aureus
7	3	Generalized peritonitis	II. Staph. aureus
8	6	Generalized peritonitis	II. Staph. aureus
9	3	Generalized peritonitis	II. Staph. aureus
10	2	Generalized peritonitis	II. Staph. aureus
11	3	Generalized peritonitis	H. Staph. aureus
12	1	Pneumonia, peritoneum glistering, no fluid	Sterile
13	3	Generalized peritonitis	H. Staph. aureus
14	1.5	Generalized peritonitis	H. Staph. aureus
15	4.5	Generalized peritonitis	H. Staph. aureus
16	1.5	Generalized peritonitis	H. Staph. aureus
17	3	Generalized peritonitis	II. Staph. aureus
18	2	Generalized peritonitis	H. Staph. aureus
19	2	Generalized peritonitis	II. Staph. aureus
20	3	Generalized peritonitis	H. Staph. aureus
21	2	Generalized peritonitis	H. Staph. aureus
22	2	Sacrificed, 7 days; peri- toneum normal appear- ance, no fluid	Sterile
23	23	Sacrificed, 7 days; ab- scess in omentum, no evidence peritonitis	Sterile
24	24	Generalized peritonitis evidence peritonitis	H. Staph. aureus
25	25	Sacrificed 3 weeks; no evidence of infection + adhesions	Sterile

lowing contamination with the hemolytic *Staphylococcus aureus*. Con-
tamination was produced in these animals following total left pneu-
mectomy.
This report is concerned with a similar series of experiments in which
the peritoneal cavities of dogs were contaminated and bacteriostatic
agents introduced immediately following introduction of the organism.

METHOD OF STUDY

Dogs which varied rather widely in weight (6 to 18 kg.) were used.
In the experiments, care was taken to distribute animals of comparable
weights among the control group and the variously treated group.
Attempts to produce generalized peritonitis in a group of animals by
injection of organisms into the peritoneal cavity failed. Localized ab-
scesses, or no apparent infection at all, occurred in many animals. The
following procedure was suggested by experiments performed by Halsted
in studies of infected wounds.
The operative procedure was the same in all experiments and was
performed under aseptic conditions. Intravenous nembutal anesthesia

TABLE IV
STREPTAZINE GROUP: 0.1 CC. FLOREN SALINE SUSPENSION OF HEMOLYTIC
STAPHYLOCOCCI IN ATRES AND 0.3 GM. STREPTAZINE PER KILOGRAM
BODY WEIGHT

EXPERIMENTAL GROUP	NO. OF ANIMALS	DATE AFTER OPERATION (DAYS)	RESULTS AT AUTOPSY, CAUSE OF DEATH	CLINICAL COURSE OF DISEASE	TREATMENT
A. Sulfadiazine 0.3 gm. per kilo.	66	11	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	67	1.5	Generalized peritonitis	Sacrificed 2 weeks; no evidence of infection;	Sterile
	68			adhesions ++	Sterile
	69			Sacrificed 3 weeks; no evidence of infection;	Sterile
	70			adhesions ++	Sterile
	71	2	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	72	2.5	Generalized peritonitis	Sacrificed 6 weeks; abscess of left upper quadrant, no peritonitis	II. Staph. aureus
	73			Sacrificed 6 weeks; abscess of left upper quadrant, no peritonitis	Sterile
	74			Sacrificed 5 weeks; subphrenic abscess, no peritonitis	Sterile
	75			Sacrificed 5 weeks; no evidence of infection;	Sterile
B. Sulfadiazine 0.3 gm. per kilo.	76	1	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	77	1.5	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	78	8	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	79	2.5	Generalized peritonitis	Sacrificed 8 weeks; no evidence of infection;	II. Staph. aureus
	80			Sacrificed 8 weeks; no evidence of infection;	Sterile
	81	2	Generalized peritonitis	Generalized peritonitis	Sterile
	82	4	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	83	2	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	84	2	Generalized peritonitis	Sacrificed 8 weeks; no evidence of infection;	Sterile
	85	2	Generalized peritonitis	Sacrificed 8 weeks; no evidence of infection;	II. Staph. aureus
	86			adhesions ++	Sterile
	87	1	Generalized peritonitis	Sacrificed 5 weeks; subphrenic abscess, no peritonitis	II. Staph. aureus
	88	1.5	Generalized peritonitis	Generalized peritonitis	II. Staph. aureus
	89			Sacrificed 4 weeks; no evidence of infection;	Sterile
				no adhesions	

drug was used in the control experiments. In the other three groups, sulfanilamide, sulfathiazole, and sulfadiazine, respectively, were employed. In each experiment 0.3 gm. of the drug per kilogram of body weight of the animal was the amount used. Coarse crystals of the drug were suspended in about 50 c.c. of sterile distilled water and poured among the loops of small intestine.

About one-half of the animals in each of the groups receiving sulfonamide therapy were also given the drug by mouth, in doses shown in Tables I to VI.

TABLE IV

SULFADIAZINE GROUP: 0.1 C.C. FLOEIS SALINE SUSPENSION OF HEMOLYTIC STAPHYLOCOCCUS AUREUS AND 0.3 GM. SULFADIAZINE PER KILOGRAM BODY WEIGHT

	EXP. NO.	DURATION OF LIFE AFTER OPERATION (DAYS)	FINDINGS AT AUTOPSY, CAUSE OF DEATH	CULTURE OF PERITONEUM AT AUTOPSY
A. Sulfadiazine 0.3 Gm. per kilogram body weight intraperitoneally	66	14	Generalized peritonitis	H. Staph. aureus
	67	1.5	Generalized peritonitis	H. Staph. aureus
	68		Sacrificed 8 weeks; no evidence of infection; adhesions ++	Sterile
	69		Sacrificed 8 weeks; no evidence of infection; adhesions ++	Sterile
	70		Sacrificed 10 weeks; no evidence of infection; no adhesions	Sterile
	71	2	Generalized peritonitis	H. Staph. aureus
	72	2.5	Generalized peritonitis	H. Staph. aureus
	73		Sacrificed 6 weeks; absence of left upper quadrant, no peritonitis; adhesions +++	Sterile
	74		Sacrificed 5 weeks; subphrenic abscess, no peritonitis; adhesions +++	Sterile
	75		Sacrificed 5 weeks; no evidence of infection; adhesions +++	Sterile
	76	1	Generalized peritonitis	H. Staph. aureus
	77	1.5	Generalized peritonitis	H. Staph. aureus
B. Sulfadiazine 0.3 Gm. per kilogram body weight intraperitoneally and 0.5 Gm. by mouth every 12 hours	78	8	Generalized peritonitis	H. Staph. aureus
	79	2.5	Generalized peritonitis	H. Staph. aureus
	80		Sacrificed 8 weeks; no evidence of infection; adhesions ++	Sterile
	81	2	Generalized peritonitis	Sterile
	82	4	Generalized peritonitis	H. Staph. aureus
	83	2	Generalized peritonitis	H. Staph. aureus
	84	2	Generalized peritonitis	H. Staph. aureus
	85		Sacrificed 8 weeks; no evidence of infection; adhesions +++	Sterile
	86		Sacrificed 5 weeks; subphrenic abscess, no peritonitis; adhesions +++	Sterile
	87	1	Generalized peritonitis	H. Staph. aureus
	88	1.5	Generalized peritonitis	H. Staph. aureus
	89		Sacrificed 4 weeks; no evidence of infection; no adhesions	Sterile

drug was used in the control experiments. In the other three groups, sulfanilamide, sulfathiazole, and sulfadiazine, respectively were employed. In each experiment 0.3 Gm. of the drug per kilogram of body weight of the animal was the amount used. Coarse crystals of the drug were suspended in about 50 c.c. of sterile distilled water and poured among the loops of small intestine.

About one-half of the animals in each of the groups receiving sulfonamide therapy were also given the drug by mouth, in doses shown in Tables I to VI.

TABLE III

SULFATHIAZOLE GROUP: 0.1 C.C. FROZEN SALINE SUSPENSION OF HEMOLYTIC STAPHYLOCOCCUS AUREUS AND 0.3 GM. SULFATHIAZOLE PER KILOGRAM BODY WEIGHT

	EXP. NO.	DURATION OF LIFE AFTER OPERATION (DAYS)	FINDINGS AT AUTOPSY, CAUSE OF DEATH	CULTURE OF PERITONEUM AT AUTOPSY
A. Sulfathiazole 0.3 Gm. per kilogram body weight intraperitoneally	45	4	Generalized peritonitis	H. Staph. aureus
	46	6	Generalized peritonitis	H. Staph. aureus
	47	4	Generalized peritonitis	H. Staph. aureus
	48	1.5	Generalized peritonitis	H. Staph. aureus
	49		Sacrificed 8 weeks; no evidence of infection, no adhesions	Sterile
	50		Sacrificed 19 weeks; no infection, no adhesions	Sterile
	51		Sacrificed 6 weeks; no evidence of infection, adhesions ++	Sterile
	52	1	Generalized peritonitis	H. Staph. aureus
	53	3.5	Generalized peritonitis	H. Staph. aureus
	54		Sacrificed 2 weeks; infection of abdominal wound, no peritonitis or adhesions	Sterile
	55	4	Generalized peritonitis	H. Staph. aureus
B. Sulfathiazole 0.3 Gm. per kilogram body weight intraperitoneally and 0.5 Gm. by mouth every eight hours	56	2	Hemorrhage from splenic vessel, no evidence of infection	Sterile
	57		Sacrificed 23 weeks; no evidence of infection, no adhesions	Sterile
	58	4	Generalized peritonitis	H. Staph. aureus
	59		Died of pneumonia, 2 days; no evidence of peritonitis	Sterile
	60	1.5	Generalized peritonitis	H. Staph. aureus
	61	3	Generalized peritonitis	H. Staph. aureus
	62	2	Generalized peritonitis	H. Staph. aureus
	63	1.5	Generalized peritonitis	H. Staph. aureus
	64	1	Generalized peritonitis	H. Staph. aureus
	65	1.5	Generalized peritonitis	H. Staph. aureus

fine silk sutures, and the skin with continuous silk. No dressing was applied to the wound.

The saline suspension of the organism was made in large quantity and was placed in Pyrex ampules in amounts of from 1 to 2 c.c. These ampules were placed in containers of alcohol, and frozen in a dry ice chamber at -78° C. Its virulence has been assayed against mice at intervals of time and found to be remarkably stable for as long as eight months. About five billion bacteria were contained in 1 c.c. of the suspension.

More than 100 animals were operated upon. Generally the animals were operated upon in groups of four, six, or eight, control experiments in which no drug was being used being performed with experiments in which the drug was employed. Four types of experiments were performed. In all, 0.1 c.c. of the organism suspension was injected. No

TABLE IV

SULFADIAZINE GROUP: 0.1 C.C. FLOTTEN SALINE SUSPENSION OF HEMOLYTIC STAPHYLOCOCCUS AUREUS AND 0.3 GM. SULFADIAZINE PER KILOGRAM BODY WEIGHT

	EXP. NO.	DURATION OF LIFE AFTER OPERATION (DAYS)	FINDINGS AT AUTOPSY, CAUSE OF DEATH	CULTURE OF PERITONEUM AT AUTOPSY
A. Sulfadiazine 0.3 Gm. per kilogram body weight intraperitoneally	66	14	Generalized peritonitis	H. Staph. aureus
	67	1.5	Generalized peritonitis	H. Staph. aureus
	68		Sacrificed 8 weeks; no evidence of infection; adhesions ++	Sterile
	69		Sacrificed 8 weeks; no evidence of infection; adhesions ++	Sterile
	70		Sacrificed 10 weeks; no evidence of infection; no adhesions	Sterile
	71	2	Generalized peritonitis	H. Staph. aureus
	72	2.5	Generalized peritonitis	H. Staph. aureus
	73		Sacrificed 6 weeks; abscess of left upper quadrant, no peritonitis	Sterile
	74		Sacrificed 5 weeks; subphrenic abscess, no peritonitis, adhesions +++	Sterile
	75		Sacrificed 5 weeks; no evidence of infection; adhesions +++	Sterile
	76	1	Generalized peritonitis	H. Staph. aureus
	77	1.5	Generalized peritonitis	H. Staph. aureus
B. Sulfadiazine 0.3 Gm. per kilogram body weight intraperitoneally and 0.5 Gm. by mouth every 12 hours	78	8	Generalized peritonitis	H. Staph. aureus
	79	2.5	Generalized peritonitis	H. Staph. aureus
	80		Sacrificed 8 weeks; no evidence of infection; adhesions ++	Sterile
	81	2	Generalized peritonitis	Sterile
	82	4	Generalized peritonitis	H. Staph. aureus
	83	2	Generalized peritonitis	H. Staph. aureus
	84	2	Generalized peritonitis	H. Staph. aureus
	85		Sacrificed 8 weeks; no evidence of infection; adhesions +++	Sterile
	86		Sacrificed 5 weeks; subphrenic abscess, no peritonitis, adhesions +++	Sterile
	87	1	Generalized peritonitis	H. Staph. aureus
	88	1.5	Generalized peritonitis	H. Staph. aureus
	89		Sacrificed 4 weeks; no evidence of infection; no adhesions	Sterile

drug was used in the control experiments. In the other three groups, sulfanilamide, sulfathiazole, and sulfadiazine, respectively were employed. In each experiment 0.3 Gm. of the drug per kilogram of body weight of the animal was the amount used. Coarse crystals of the drug were suspended in about 50 c.c. of sterile distilled water and poured among the loops of small intestine.

About one-half of the animals in each of the groups receiving sulfonamide therapy were also given the drug by mouth, in doses shown in Tables I to VI.

Animals that died less than twenty-four hours after operation are not included in this study.

Samples of blood for determination of the drug concentration were obtained at occasional intervals. The blood concentration determinations were recorded in milligrams per 100 c.c. of blood. Average blood

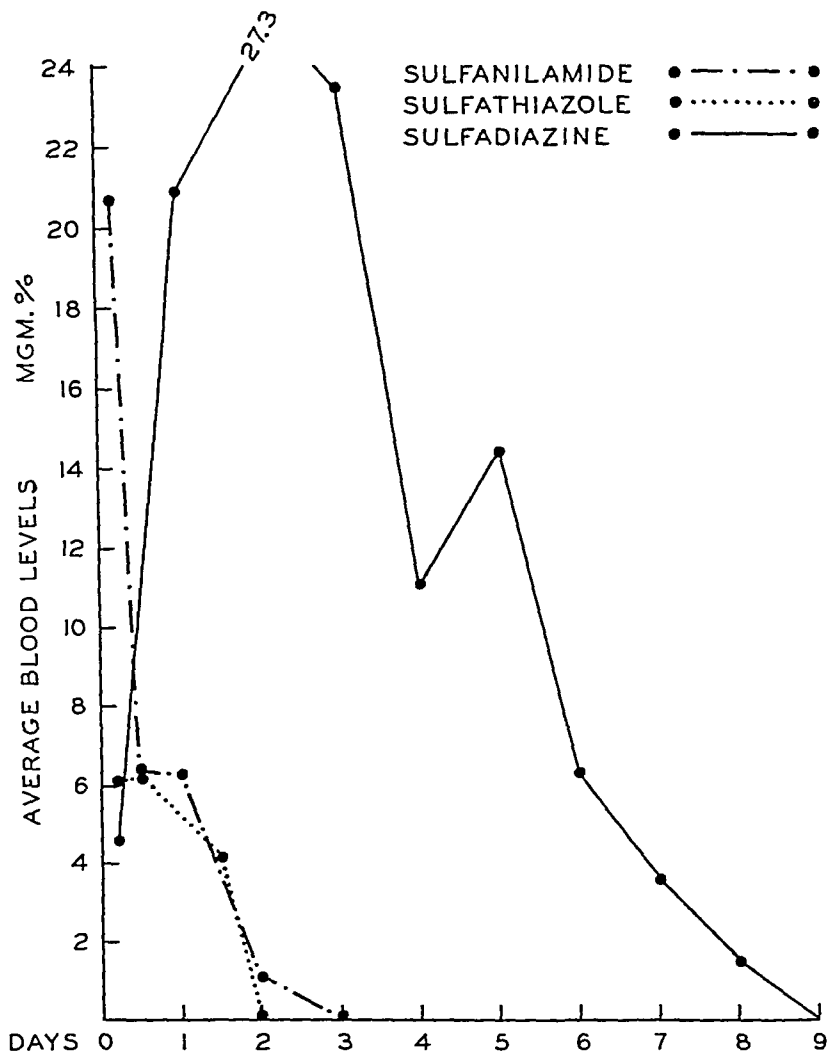


Fig. 1.—Graphic representation of the effects of local implantation of the sulfonamide drugs on blood concentration. Average figures are recorded in milligrams per 100 c.c. of blood.

levels were computed, and the curve of the levels obtained in the experiments in which the drug was administered locally, but not by mouth, is shown in Fig. 1.

Animals that received the drug by mouth were given 0.5 Gm. twice or three times daily. If the animal survived, administration of the drug was continued for ten days. Daily blood levels were recorded, and in all

TABLE V

SUMMARY OF TABLE II, III, AND IV, SHOWING FATE OF SUBGROUPS A AND B IN EACH GROUP

	NUMBER TOTAL OF DOGS	NUMBER DIED OF PERITONITIS	NUMBER SACRIFICED OR DIED OF OTHER CAUSES	PER CENT DYING OF PERITONITIS	AVERAGE DURA- TION OF LIFE OF ANIMALS DYING OF PERITONITIS (DAYS)
II (A) Sulfanilamide locally	11	7	4	63.3	5.3
II (B) Sulfanilamide locally, + 0.5 Gm. by mouth every eight hours	8	2	6	25.0	3.0
III (A) Sulfathiazole locally	11	7	4	63.5	3.4
III (B) Sulfathiazole locally + 0.5 Gm. by mouth every eight hours	10	7	3	70.0	2.1
IV (A) Sulfadiazine locally	12	6	6	50.0	4.3
IV (B) Sulfadiazine locally + 0.5 Gm. by mouth every 12 hours	12	8	4	66.7	3.8

TABLE VI

SUMMARY OF FATE OF ENTIRE GROUP OF ANIMALS INOCULATED WITH HEMOLYTIC STAPHYLOCOCCUS AUREUS

	TOTAL NUMBER OF ANIMALS	NUMBER DIED OF PERITO- NITIS	NUMBER SACRIFICED OR DIED OF OTHER CAUSES	PER CENT DYING OF PERITO- NITIS	AVERAGE DURA- TION OF LIFE OF ANIMALS DYING OF PERITONITIS (DAYS)
Control, no drugs- used	25	21	4	84.0	3.4
Sulfanilamide group	19	9	10	47.4	4.5
Sulfathiazole group	21	14	7	66.6	2.8
Sulfadiazine group	24	11	10	58.3	4.0

experiments the blood concentration remained high (above 5 mg. per 100 c.c. blood) but varied from day to day.

RESULTS

The effects of sulfanilamide, sulfathiazole, and sulfadiazine on the uncontaminated peritoneum of dogs have been reported by us previously.²

The comparative effects of these drugs upon hemolytic *Staphylococcus aureus* infections of the pleural cavity, following pneumonectomy, have also been reported.¹ In the latter article sulfathiazole was found to be more effective in the prevention of empyema in dogs than were the other two drugs. It is surprising, therefore, that fatal peritonitis occurred in a greater percentage of instances in this group of experiments when sulfathiazole was used than when either sulfanilamide or sulfadiazine was used.

The very low mortality rate in the group of animals which received sulfanilamide therapy both locally and by mouth is of interest.

The numbers of animals used in the various subgroups are not great, however, and we believe that one is not justified in the conclusion that any of these drugs is greatly superior to another for the prevention of infections in wounds contaminated with the hemolytic *Staphylococcus aureus*.

The blood concentration curves follow very closely the same form as those obtained with the implantation of sulfanilamide, sulfathiazole, and sulfadiazine in the normal peritoneal cavity. The rate of absorption appears to be slightly prolonged with all three drugs and, as has been previously shown, the rate of excretion of sulfadiazine is much slower than with the other drugs.

Adhesions between loops of small bowel were in general much more numerous and more dense in animals that recovered after sulfadiazine therapy than in those in which sulfanilamide or sulfathiazole was used.

SUMMARY

1. The effects of sulfanilamide, sulfathiazole, and sulfadiazine in the prevention of hemolytic *Staphylococcus aureus* infection of the peritoneum have been studied in the dog.

2. The drugs were applied locally immediately after contamination of the peritoneal surface with carefully measured numbers of the organisms. A number of animals were also given the drug by mouth.

3. Total generalized peritonitis occurred most frequently in the group of animals treated with sulfathiazole and least frequently in those treated with sulfanilamide. The lowest mortality rate in any group occurred in animals treated by means of sulfanilamide given by mouth in addition to local application of the drug.

REFERENCES

1. Daniel, R. A., Jr., Billings, F. T., and Crutcher, R. R.: The Local Effect of Sulfanilamide, Sulfathiazole and Sulfadiazine Upon Hemolytic *Staphylococcus Aureus* Infections of the Pleural Cavity, *Ann. Surg.* 117: 670, 1943.
2. Crutcher, R. R., Billings, F. T., and Daniel, R. A., Jr.: The Effect of Sulfanilamide, Sulfathiazole, and Sulfadiazine Upon the Peritoneum, *Ann. Surg.* 117: 685, 1943.
3. Halsted's Surgical Papers, Vol. 1, Baltimore, 1924, Williams & Wilkins Company, p. 102.

CERTAIN SULFOXAMIDE DRUGS AND CERTAIN DERIVATIVES OF ASCORBIC ACID IN EXPERIMENTAL GAS GANGRENE IN WOUNDED MICE

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IN TESTING chemotherapeutic agents against gas gangrene in animals a wide variety of assay procedures have been used. Some investigators have induced gas gangrene by the injection of whole cultures of pathogenic clostridia into the muscles of their experimental animals. Others, attempting to simulate the mode of infection of war wounds, have surgically traumatized the muscles and have introduced clostridia into these lesions. The result has been, as Sandusky and Meleney¹ have pointed out, a diversity of opinion on the value of chemotherapy. Likewise, various species of animals have been used as assay organisms. Perhaps the most economical of these is the mouse. The usual procedure in infecting mice has been the injection of whole cultures of clostridia into the thigh. However, in view of the criticisms raised by Sandusky and Meleney we felt it was desirable to develop a procedure for wounding and infecting mice in order to assay compounds against gas gangrene. Our procedure consists in the infection of exposed and crushed thigh muscles and the subsequent treatment of the wound with a powdered drug. The conditions were chosen to obtain under experimental conditions some of the traumatic and temporal characteristics of war wounds.

A number of investigators²⁻⁴ have found that sulfadiazine and sulfathiazole were the most effective of the sulfonamide drugs for the treatment of experimental gas gangrene in mice. Consequently, we have assayed these compounds by our procedure. For comparison with our method of assay we also followed the procedure used by McKee, Hamre, and Rake⁴ and injected solutions of sulfonamides, after a previous injection of clostridia and CaCl_2 , into the unwounded thighs of mice.

It was observed in the course of studies on the nutritional requirements of *Clostridium perfringens* that in vitro growth was inhibited by high concentrations of ascorbic acid. Other investigators⁵ have reported success in the use of vitamin C against certain infectious diseases. We therefore also investigated the chemotherapeutic action against gas gangrene of ascorbic acid and some of its derivatives.

ASSAY PROCEDURE

The culture medium for all strains of clostridia tested contained 0.25 per cent sodium chloride, 0.1 per cent sodium bicarbonate, 0.34 per cent disodium phosphate, 0.082 per cent monopotassium phosphate, 0.5 per cent glucose, 2 per cent Bacto-tryptose, 0.3 per cent Bacto-yeast extract, and 0.1 per cent sodium thioglycolate; pH 7.4. Incubation was at 37° C.

Mice weighing between 20 and 30 Gm. were anesthetized by a subcutaneous injection of nembutal (0.005 c.c. of a solution, containing 25.4 mg. per cubic centimeter of distilled water, per gram of body weight). The extensor muscles of the thigh were exposed by an incision about 5 mm. long, and the appropriate amount of a whole culture of clostridia was injected into the vastus lateralis. The belly of the extensor muscles was then crushed with a fine hemostat for about 3 mm. of its length. After one-half hour about 5 mg. of the compound to be tested were spread into the wound and the incision was closed with a cotton suture. Independent tests showed that the compounds used were not lethal in dosages several times those employed in therapy.

The operation itself was not lethal since all of fourteen mice survived when infection was not attempted. In addition, no deaths occurred in twenty-seven cases where infection was attempted with 0.5 c.c. of old (twenty-four to thirty-hour) cultures of *Clostridium perfringens*.

A six-hour culture of *Clostridium perfringens* in our medium consists of vegetative cells in the logarithmic phase of growth. No spores are formed due to the presence of sugar. When 0.05 c.c. of a six-hour culture of *Clostridium perfringens* (A.T.C.C. No. 846) was injected without subsequent therapy, 100 per cent of eighteen animals died; with 0.03 c.c., 90 per cent of thirty-eight died; with 0.025 c.c., 75 per cent of fifty-nine died. Most of the deaths among infected animals occurred within twenty-four hours and all within forty-eight. Before death the mice exhibited hematuria. The appearance of the dead animals at autopsy was characteristic of the infective organism.^{6, 7} Direct smears of the peritoneal fluid of the dead animals showed a predominance of gram-positive perfringens-like organisms.

The deaths were not caused by the culture medium after it had supported the growth of *Clostridium perfringens*. A six-hour culture was filtered through sintered glass under nitrogen. Eight mice survived injection of 0.05 c.c. of this filtrate into their operated thighs. Moreover, all of three animals survived intraperitoneal injections of the same material.

It was possible to kill mice by simply dropping the culture into the incision before the muscles were crushed (that is, without injecting the bacteria into the muscle). However, it was thought that the assay would be more rigorous by admitting bacteria into the connective tissue muscle sheaths. Care was taken to make the operation and infection as constant as possible from experiment to experiment. Nevertheless, there must

have been some variation in the amount of muscle injury and the extent of bacterial invasion.

Other gas gangrene organisms were employed as wound contaminants. When the wounds were infected with *Clostridium septicum* (A.T.C.C. No. 680), *Clostridium histolyticum* (A.T.C.C. No. 6282), or *Clostridium norgi* (A.T.C.C. No. 3540) eighteen-hour cultures were used, while six-hour cultures of *Clostridium sordellii* (Meleny No. 9678) were employed. Between 0.01 and 0.03 c.c. of whole cultures of these organisms was sufficient to kill all of the mice. The appearance of the dead animals upon autopsy was characteristic of the infective organism.^{1, 2} Toxins in the culture medium were not responsible for the death of the mice since 0.05 c.c. of sterile filtrates (sintered glass) in each case did not kill any of five mice.

Four different strains of mice were used in these experiments. The CF 1, the C 58, and the P. and S. mice were highly inbred, while the Columbia mice were not genetically homogeneous. In each experiment some mice served as controls and were subjected to the operation and contamination; they were sutured after one-half hour without further treatment. Those in the experimental group received a treatment with the compound indicated. In about 5 per cent of the cases mice failed to recover from the nembutal anesthesia. These animals were, of course, excluded from the experiment.

RESULTS

Table I shows the effect of sulfathiazole and sulfadiazine when applied to wounds infected with *Clostridium perfringens* by our procedure. Sulfathiazole was ineffective in two strains of mice but in the CF 1 strain resulted in a survival that was significantly different from that in the controls (χ^2 test with Yates correction, $P = < 0.01$).⁸ Sulfadiazine, on the other hand, saved significant numbers of both CF 1 and Columbia mice ($P = 0.04$ and < 0.01 , respectively). In many cases large lesions on the thighs of the sulfonamide drug-treated survivors persisted for several weeks until the experiments were terminated.

TABLE I

THE EFFECT OF SULFONAMIDE DRUG POWDER IN WOUNDS OF MICE CONTAMINATED WITH *Clostridium Perfringens*

COMPOUND	SOURCE OF MICE	CONTROLS		EXPERIMENTALS	
		NUMBER OF MICE	PER CENT SURVIVAL	NUMBER OF MICE	PER CENT SURVIVAL
Sulfathiazole	Columbia	16	13	26	19
Sulfathiazole	C 58	10	30	15	20
Sulfathiazole	CF 1	14	0	30	63
Sodium sulfadiazine	Columbia	18	17	36	50
Sodium sulfadiazine	CF 1	15	7	30	67

Results were somewhat different when infection was attempted by the procedure used by McKee, Hamre, and Rake.⁴ An injection of

0.05 c.c. of a six-hour culture of *Clostridium perfringens* (a 10^{-1} or 2×10^{-1} dilution in a broth containing the appropriate amount of Ca Cl_2) into the unwounded thighs of Columbia mice was followed after one-half hour by 0.1 c.c. of water containing either 1 mg. of sulfathiazole or 1 mg. of sulfadiazine. Among the sulfathiazole-treated animals 60 per cent of thirty-one mice survived, which was not significantly different from the 53 per cent of the fifteen mice that survived among the controls. However, sulfadiazine resulted in the survival of 97 per cent of thirty mice, which is significantly different from the controls ($P = < 0.01$). Whether the Ca Cl_2 injured the bacteria as well as the muscle into which it was injected is not known.

In Columbia mice infected with *Clostridium perfringens*, l-ascorbic acid resulted in a survival that was statistically different ($P = < 0.01$) from that of the controls (Table II). This was not the case in the other strains of mice. When sodium ascorbate powder was used no significant increase in survival over the controls was obtained. However, ascorbic acid is very labile in neutral solutions. In order to obtain indirect evidence as to whether the effect of l-ascorbic acid was due simply to its acidity, the action of a compound with a similar dissociation constant, succinic acid, was investigated. In two experiments where 25 per cent of eight controls survived, 61 per cent of eighteen treated animals lived. This is not a significant difference ($P = 0.2$), and suggests that ascorbic acid does not work solely by virtue of its acidic properties.

TABLE II

THE EFFECT OF L-ASCORBIC ACID AND SOME DERIVATIVES IN WOUNDS OF MICE CONTAMINATED WITH *Clostridium Perfringens*

COMPOUND	SOURCE OF MICE	CONTROLS		EXPERIMENTALS	
		NUMBER OF MICE	PER CENT SURVIVAL	NUMBER OF MICE	PER CENT SURVIVAL
l-ascorbic acid	Columbia	33	9	60	40
l-ascorbic acid	P. and S.	10	30	24	24
l-ascorbic acid	C 58	9	10	17	11
Sodium ascorbate	Columbia	20	20	35	31
Dehydroascorbic acid	Columbia	8	12	18	0
l-isoascorbic acid	C 58	19	10	30	37
d-glucosascorbic acid	C 58	5	20	10	10

Low concentrations of l-ascorbic acid may produce redox potentials in wounds favorable for the growth of anaerobes.⁹ This factor may antagonize the therapeutic action of ascorbic acid and account for the failure of some of the mice to survive after treatment. Hence the action of dehydroascorbic acid was investigated but this compound was not effective. The great lability of dehydroascorbic acid unfortunately makes the result equivocal. Other analogues of ascorbic acid were also tested. No effect was obtained with d-glucosascorbic acid but l-isoascorbic acid resulted in an increased survival among the experimental animals which may be significant ($P = 0.06$).

A few attempts to save infected mice by previous feeding with high concentrations of l-ascorbic acid (1 mg. of neutralized ascorbic acid per day for nine days) failed. Likewise, subcutaneous injection of neutralized solutions of ascorbic acid and injection into the vastus lateralis after contamination were without effect.

TABLE III

THE EFFECT OF SULFONAMIDE DRUGS AND ASCORBIC ACID IN WOUNDS OF COLUMBIA MICE CONTAMINATED WITH WHOLE AND WASHED CULTURES OF *Clostridium Septicum*, *Clostridium Histolyticum*, *Clostridium Novyi*, AND *Clostridium Sordellii*

TREATMENT	ORGANISM							
	SEPTICUM		HISTOLYTICUM		NOVYI		SORDELLII	
	NUM- BER OF MICE	PER CENT SUR- VIVAL	NUM- BER OF MICE	PER CENT SUR- VIVAL	NUM- BER OF MICE	PER CENT SUR- VIVAL	NUM- BER OF MICE	PER CENT SUR- VIVAL
<i>Whole Culture</i>								
Control	5	0	9	0	5	0	5	0
l-Ascorbic acid	9	0	17	12	8	0	10	0
Sulfathiazole	9	22	17	18	9	0	10	10
Sodium sulfadiazine	9	0	17	18	7	0	10	0
<i>Washed Culture</i>								
Control	3	0	5	0	5	0	5	0
l-Ascorbic acid	7	0	10	0	10	0	9	0
Sulfathiazole	9	0	10	0	9	11	10	0
Sodium sulfadiazine	8	0	10	0	10	20	10	0

Some preliminary experiments on the chemotherapy of *Clostridium septicum*, *Clostridium histolyticum*, *Clostridium novyi*, and *Clostridium sordellii* infections in Columbia mice are reported in Table III. Neither l-ascorbic acid, sulfathiazole, nor sulfadiazine, after the injection of whole cultures, resulted in significant increases in survival over the controls. These negative results cannot be due to the presence of toxins in our cultures. In the first place, as mentioned before, sterile filtrates of these cultures were not toxic. To further test this point, cells which were twice resuspended in fresh culture medium, and hence washed free of their metabolic products, were used as contaminants. As Table III shows, the response to therapy remained the same as when whole cultures were used. None of the differences shown in Table III have a P of < 0.2 .

DISCUSSION

Perhaps the most interesting conclusion to draw from these results is that the value of chemotherapy depended in some way upon the strain of mice used for the experiment. For example, sulfathiazole and l-ascorbic acid were effective in some strains of mice but not in others. Discrepancies among the results obtained with chemotherapy by other investigators may be accounted for to some extent by differences in the strain of experimental animals used. Sulfadiazine was the only compound investigated which was successful against gas gangrene in

at least two different strains of mice. This result is in accord with the fact that, of the sulfonamide drugs, sulfadiazine has been the most generally effective against experimental gas gangrene in the hands of other investigators.^{1-4, 10, 11}

If, however, a drug can be effective in one strain of mice and not another, it is not surprising that results from animal experiments have not predicted with accuracy the results in man. For example, the sulfonamide drugs have been disappointing in the treatment of gas gangrene in World War II.¹² Therefore, the partial success we have obtained by the use of ascorbic acid in mice infected with *Clostridium perfringens* can be, at the most, only suggestive.

Mice are not known to require ascorbic acid in their diet but the therapeutic dose used in the wounds was, gram for gram of body weight, far above the daily nutritional requirement of the guinea pig and man. However, a case of vitamin C hypervitaminosis is unknown.⁵ Ascorbic acid has been known to be effective in various ways in the treatment of other infectious diseases,⁵ but there is no evidence from our work to describe its mode of action against *Clostridium perfringens*.

SUMMARY

1. A method is described for wounding and infecting mice with various strains of pathogenic clostridia.

2. In two strains of mice the local application of sulfadiazine saved about 60 per cent of the animals infected with *Clostridium perfringens*, a significant difference from the controls.

3. Sulfathiazole was also effective against *Clostridium perfringens* in one strain of mice but not in others.

4. In one strain of mice ascorbic acid saved about 40 per cent of the animals infected with *Clostridium perfringens*, a significant difference from the controls. However, it was ineffective against gas gangrene in other strains.

5. Ascorbic acid, sulfadiazine, and sulfathiazole were ineffective against infections caused by *Clostridium novyi*, *Clostridium histolyticum*, *Clostridium sordellii*, and *Clostridium septicum*.

This work was supported by a grant from the Josiah Macy, Jr. Foundation. We are indebted to Dr. L. C. Dunn and Dr. S. Schoenheimer for supplying the Columbia and CF 1 mice, and to Dr. E. C. MacDowell and Dr. V. Bryson for the C 58 mice. We also wish to thank Dr. Frank L. Meleney for his valuable discussion and for supplying us with the culture of *Clostridium sordellii*.

REFERENCES

1. Sandusky, W. R., and Meleney, F. L.: Experimental Gas Gangrene, Arch. Surg. 45: 890, 1942.
2. Bliss, E. A., Long, P. H., and Smith, D.: Chemotherapy of Experimental Gas Gangrene and Tetanus Infections in Mice, War Med. 1: 799, 1941.
3. Hac, L. R., and Hubert, A. C.: Use of Sulfonamides in Treatment of Experimental *Clostridium Welchii* Infection, Proc. Soc. Exper. Biol. & Med. 53: 53, 1943.
4. McKee, C., Hamre, D. M., and Rake, G.: Action of Antibiotics on Organisms Producing Gas Gangrene, Proc. Soc. Exper. Biol. & Med. 54: 211, 1943.

5. Rosenberg, H. R.: *Chemistry and Physiology of the Vitamins*, New York, 1942, Interscience Publishers, Inc.
6. Melency, F. L.: *The Bacteriologic and Immunologic Aspects of Surgery*, Nelson's Loose Leaf Surgery, Vol. 1, Chapter 111, New York, 1941, Thomas Nelson and Sons.
7. Committee on Anaerobic Bacteria and Infections: *Report on the Anaerobic Infection of Wounds and the Bacteriological and Serological Problems Arising Therefrom*, Medical Research Committee (Great Britain) Special Report Series 39, London, 1919, His Majesty's Stationery Office.
8. Fisher, R. A.: *Statistical Methods for Research Workers*, Ed. 8, London, 1941, Oliver & Boyd, Ltd.
9. Reed, G. B., and Orr, J. H.: *Cultivation of Anaerobes and Oxidation-Reduction Potential*, *J. Bact.* 45: 309, 1943.
10. Reed, G. B., and Orr, J. H.: *Local Chemotherapy of Experimental Gas Gangrene*, *War Med.* 2: 59, 1942.
11. Sewell, R. L., Dowdy, A. H., and Vincent, J. G.: *Chemotherapy and Roentgen Radiation in Clostridium Welchii Infections: Clinical and Experimental Studies*, *Surg., Gynec. & Obst.* 74: 361, 1942.
12. MacLennan, J. D.: *Anaerobic Infections of War Wounds in the Middle East*, *Lancet* 2: 63, 91, 123, 1943.

THE EFFICACY OF HEPARIN ADMINISTERED BY INTRAVENOUS, INTRAMUSCULAR, AND SUBCUTANEOUS ROUTES AND A STUDY OF THE EFFECT OF FIVE BACTERIOSTATIC AGENTS ON HEPARIN ACTION

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THERAPEUTIC administration of heparin to be ideal should result in a prolonged, constant, and controllable elevation of the coagulation time of venous blood. Single intravenous injections result in a marked, but unsustained, rise in coagulation time. Intramuscular injections give a more controllable effect, which is preferable for therapy. The peak of the anticoagulant effect is less extreme and it develops longer after administration. The intramuscular use of heparin has not been widely adopted hitherto because of the high cost. The potentiation of the action of heparin by small doses of dicumarol^{2, 7} makes it possible to use the intramuscular route with greater economy.

The response to standard intramuscular injections of heparin has been studied in a group of adults and compared with that of the intravenous and subcutaneous injection of heparin. The local reaction to injected heparin has been studied using heparin in physiologic saline solution as a control and heparin with five different preservatives. Both the local reaction produced and the effectiveness of the preparation in coumarinized and noncoumarinized individuals have been considered. Because of the possibility of contamination, we have preferred not to use heparin without a preservative for routine purposes.

Subcutaneous administration of heparin gives results similar to those obtained with intramuscular administration. However, it gives the patient greater discomfort and there is usually an area of induration and tenderness which persists for twenty-four hours. Heparin is inactive when administered orally.

Two substances, benzidine and protamine, have been found to inhibit the action of heparin when injected coincidentally with heparin.^{1, 3} Of the five preservatives studied here, namely phenol, tricresol, merthiolate, phenylmercuric borate, and chlorobutanol, none seemed to have any inhibitory effect in the concentration used.

METHODS

An unselected group of patients with vascular pathology requiring anticoagulant therapy was studied.

We are indebted to the Lederle Laboratories, Inc., Pearl River, N. J., for the heparin preparations tested.

Received for publication, Aug. 4, 1944.

A given dose of heparin was administered and the coagulation time of venous blood determined by the method of Lee and White⁴ at thirty, sixty, ninety, and 120 minutes after the time of injection.

Heparin was injected intravenously in 50 mg. doses in a few cases, but usually in 10 to 20 mg. doses. Intramuscular injections of 50 mg. were made into the gluteus muscles. Subcutaneous injections of 50 mg. were made into the subcutaneous tissue of thigh, flank, abdomen, and back.

Heparin solutions used all contained 10 mg. per milliliter⁵ of the sodium salt of heparin. The preservatives used were phenol, 0.5 per cent; chlorobutanol, 0.5 per cent; phenylmercuric borate, 0.004 per cent; merthiolate, 0.01 per cent; and trieresol, 0.3 per cent. Heparin in physiologic saline solution was used as a control.

The local reaction to intramuscular and subcutaneous injection was judged subjectively and objectively. Subjectively, patients were questioned as to soreness immediately upon injection, twelve hours after injection, and twenty-four hours after injection. Objectively, the areas of induration and erythema, if any, were measured at twelve hours and at twenty-four hours. Wherever possible, each patient was given injections with as many different preservatives as possible, both intramuscularly and subcutaneously, at some time in this course of treatment.

RESULTS

Intravenous injection of heparin resulted in a sharp rise in coagulation time within five minutes. An injection of 50 mg. caused an elevation of coagulation time to between 200 and 250 minutes, and an injection of 20 mg. raised the coagulation time to between 100 and 120 minutes. The coagulation time returned to normal within one to two hours.

Intramuscular injection of 50 mg. of heparin caused a slower elevation of coagulation time, and the elevation was less marked than on

TABLE I
COAGULATION TIMES FOLLOWING THE INTRAVENOUS ADMINISTRATION OF HEPARIN

PATIENT	DOSAGE (c.c.)	VENOUS COAGULATION TIME IN MINUTES			
		BEFORE INJECTION	AFTER INJECTION		
		0 MIN.	30 MIN.	60 MIN.	90 MIN.
I. L.	1	15		60	30
J. H.	1	20		65	35
R. J.	1	15	80	45	
S. L.	2	20	180	100	25
A. G.	2	15	125	90	30
A. C.	1	12	85	60	30
W. M.	1	12		80	
G. W.	2	15	110	80	30
M. C.	1	20	110	100	20
Average	1.3	16	115	75.5	28.5

TABLE II

COAGULATION TIME OF VENOUS BLOOD IN MINUTES AFTER INTRAMUSCULAR
INJECTION OF 5 C.C. OF HEPARIN

	PATIENT NO.	BEFORE INJECTION	AFTER INJECTION			
			30 MIN.	60 MIN.	90 MIN.	120 MIN.
Heparin in 1/25,000 phenylmercuric borate	21	25	30	45		25
	9	18	32	47	35	
	24	20	37	47	28	
	30	10	42	55		
	30	25	50	60		
	2	20		60	35	
	18	20	35	48	35	
	22	15	35	45		
	Average	19	37	51	33	25
Heparin in physiologic saline solution	15	15	25	35	20	
	16	15				20
	8	15	30	40		30
	14	18	32	42	30	
	4	20	40	50	20	
	29	20	32	45	90	
	7	20	32	50	30	
	2	20		50	35	
	18	20	33	48	35	
	32	15	32	50		
	22	15	35	45		
	Average	17.5	32	45.5	37	25
Heparin in 0.5 per cent phenol	25	18	32	48	20	
	5	10		60		
	6	10		50		
	Average	13	32	53	20	
Heparin in 1/10,000 merthiolate	17	15	33	46	28	
	26	18	35	48		23
	19	16	30	40		21
	27	20	35	45		
	2	20		55	40	
	17	20	35	50	35	
	10	20	25	45		
	32	20	32	50		
	Average	19.5	32	47.0	34	22
Heparin in 0.3 per cent trichresol	22	18	35	50		
Heparin in 0.5 per cent chlorobutanol	21	15	27	45	32	
	31	18	32	45		23
	Average	16.5	28.5	45	32	23

intravenous injection. The coagulation time rose to an average of 32.8 minutes one-half hour after injection and to 47.5 minutes one hour after injection. The coagulation time had returned to normal within two to two and one-half hours after the time of injection.

Subcutaneous injection of 50 mg. of heparin gave essentially the same results as an intramuscular injection.

The presence of the various preservatives in the strengths used seemed to have no demonstrable effect on the action of heparin, for in all cases the elevation of coagulation time was similar to that observed when heparin was used in physiologic saline solution.

Furthermore, the preservatives had no effect on the potentiation of heparin action by dicumaryl, for the same degree of potentiation appeared using heparin in physiologic saline solution and heparin with the various preservatives.

The intravenous use of heparin gave no immediate or delayed pain nor any objective sign of reaction in the vein.

The intramuscular injection of heparin in physiologic saline solution and in chlorobutanol caused only a slight aching sensation at the moment of injection and only a slight residual soreness twelve to twenty-four hours after the time of injection. There was no erythema nor induration at the site of injection.

Intramuscular injections of heparin in phenol, phenylmercuric borate, merthiolate, and trieresol were slightly more painful immediately, and resulted in a deep soreness and induration that was marked at the end of twenty-four hours, disappearing in most cases after forty-eight hours. There were four instances of severe local reaction with erythema and edema of one-half the gluteal region persisting for five to seven days after injection. Two of these reactions appeared after heparin was given in phenol and two after heparin in phenylmercuric borate, all four occurring in patients who were fully coumarinized and who had been getting intramuscular gluteal injections of heparin every sixth hour for seven to ten days.

In contrast to these, twelve patients in the present series received heparin in the same dosage while fully coumarinized for periods of twelve to sixteen days without untoward local reaction. The heparin used contained the less irritating preservatives.

TABLE III

COAGULATION TIME OF VENOUS BLOOD IN MINUTES AFTER SUBCUTANEOUS INJECTION OF 5 CC. OF HEPARIN

	PATIENT NO.	BEFORE INJECTION	AFTER INJECTION			
			30 MIN.	60 MIN.	90 MIN.	120 MIN.
Heparin in 1/10,000 merthiolate	12	18	25	40		25
Heparin in 0.3 per cent trieresol	1	20	32	45	35	
	12	18	28	42		
	1	21	31	45	30	
	Average	19.2	29.0	43	32.5	
Heparin in phenylmercuric borate 1/25,000	12	15	25	40		22
	12	18	30	40		28
	1	20	35	45	35	
	Average	17.6	30	41.6	35	30
Heparin in physiologic saline solution	1	20	32	45	35	
	22	18	38	44		
	Average	19	35	44.5	35	
Heparin in 0.5 per cent chlorobutanol	12	15	25	40		25
	1	20	32	42	32	
	Average	17.5	28.5	41	32	25

TABLE IV
COAGULATION TIME OF VENOUS BLOOD AFTER INTRAMUSCULAR INJECTIONS OF 5 C.C. OF HEPARIN

	PATIENT NO.	BEFORE INJECTION (MIN.)	BEFORE COUMARINIZATION				BEFORE INJECTION (MIN.)	AFTER COUMARINIZATION				PLASMA PROTHROMBIN CONCENTRATION (% OF NORMAL)
			30 MIN.	60 MIN.	90 MIN.	120 MIN.		30 MIN.	60 MIN.	90 MIN.	120 MIN.	
Heparin in 0.5 per cent phenol	25	18	32	18	20		18	55	60		12	25
	5	10		15	20		10		55		50	35
	Average	14	32	17	20		14	55	58		16	
Heparin in 1/10,000 merthiolate	17	18	32	17	27		22	50	110	90		20
	26	18	32	18		27	25	60	90		60	20
	19	18	30	10		22	20	55	80		10	30
Heparin in 1/25,000 phenylmercuric borate	Average	18	31	15	27	25	23	55	93	90	50	
	21	15	32	16		25	25	50	90		70	10
	9	18	31	17	35		20	60	90	60		10
Heparin in physiologic saline solution	11						22	15	70			15
	31						23	60	90	18		50
	21	20	36	17	28		25	50	100	65		40
Heparin in physiologic saline solution	Average	18	32	17	31	25	23	53	88	58	70	
	15	15	25	30	20		25	15	90	60	35	10
	16	20	10	50	20		20	60	90	15	30	20
Heparin in 0.5 per cent chlorobutanol	4	20	32	15	30		25	55	90	60		15
	29	20	33	50	30		25	55	90	60		10
	7	20	33	50	30		27	55	90	50		10
Heparin in 0.5 per cent chlorobutanol	Average	19	32	14	25		24	51	90	51	13	
	21	18	32	48		25	25	50	90		70	10

Three patients received intramuscular and subcutaneous heparin daily for periods ranging from two to four months without marked local reaction.

Subcutaneous injection of 50 mg. in physiologic saline solution and in chlorobutanol gave more immediate pain and more tenderness with some induration after twenty-four hours than the same preparations used intramuscularly.

Subcutaneous injection of heparin in phenol, phenylmercuric borate, merthiolate, and trieresol gave severe immediate pain and marked tenderness and induration lasting twenty-four to forty-eight hours after injection.

DISCUSSION

The intravenous use of heparin as a continuous drip can be used to maintain elevation of blood coagulation time,^{5,6} but the method subjects the patient to the inconvenience of a continuous intravenous drip and the coagulability is not easily maintained within the therapeutic range. The coagulation time rises sharply within five minutes after single injections and frequently goes beyond the range which we usually maintain (thirty to forty minutes). The average coagulation time, thirty minutes after the intravenous injection of 10 mg. of heparin, was 115 minutes.

Intramuscular administration of heparin results in a smaller, more manageable alteration of blood coagulability and the simultaneous use of oral dicumarol permits the use of smaller amounts of heparin, making the method economically more practicable. The discomfort caused by four intramuscular injections of heparin spaced over a twenty-four hour period is not excessive and most patients tolerate the procedure well.

The subcutaneous route of heparin administration has no advantage over the intramuscular route as far as the therapeutic action of heparin is concerned. This form of administration is very painful and gives rise to fairly marked local reactions. For these reasons we feel the subcutaneous route is not to be recommended.

Of the five preservatives, phenol, trieresol, phenylmercuric borate, merthiolate, and chlorobutanol, studied in the course of this investigation, chlorobutanol seems to cause the least local reaction and to be the agent of choice. The use of heparin in physiologic saline solution is presumably attended by greater danger of infection because of the lack of bacteriostatic action. None of the five preservatives in the dilutions used caused any alteration of heparin action or of the potentiation of heparin action by oral dicumarol.

CONCLUSIONS

1. Of the three parenteral routes of heparin administration studied, that is, intravenous, intramuscular, and subcutaneous, the route of

choice would seem to be the intramuscular because of a slow, relatively even rate of absorption. This is made more practicable by the coincident oral administration of dicumarol to maintain an effective plasma prothrombin concentration of 20 to 30 per cent of normal, thus reducing the amount of heparin needed to maintain a venous coagulation time of thirty to forty minutes.

2. Of the five preservative agents studied, phenol, 0.5 per cent; tricresol, 0.3 per cent; merthiolate, 0.01 per cent; phenylmercuric borate, 0.004 per cent; and chlorobutanol, 0.5 per cent, the agent of choice for intramuscular injections is chlorobutanol because it produced the least local reaction.

REFERENCES

1. Jaques, L. B., Charles, A. F., and Best, C. H.: The Administration of Heparin, *Acta med. Scandinav. (Suppl.)*, 90, 1938.
2. Rhoads, J. E., Walker, J., and Panzer, L.: Control of Blood Coagulability With Coumarin and Other Drugs, *Northwest Med.* 42: 182, 1943.
3. Chargaff, E., and Olson, K. B.: Action of Heparin and Other Anticoagulants: The Influence of Protamine on the Anticoagulant Effect, *J. Biol. Chem.* 122: 153, 1938.
4. Lee, R. I., and White, P. H.: A Clinical Study of the Coagulation Time of Blood, *Am. J. M. Sc.* 145: 495, 1913.
5. Ravdin, I. S., and Wood, F. C.: Successful Removal of Saddle Embolus of Aorta Eleven Days After Acute Coronary Occlusion, *Ann. Surg.* 114: 834, 1941.
6. Ravdin, I. S.: Heparin, *Am. J. M. Sc.* 201: 299, 1941.
7. Walker, J., and Rhoads, J. E.: Effect of Dicumarol on Susceptibility to Action of Heparin, *SURGERY* 15: 859, 1944.

THE ALLERGIC PATHOGENIC MECHANISM OF THYROTOXICOSIS

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THIS communication will review certain pertinent factual knowledge concerning thyrotoxic disease (such as exophthalmic goiter and Basedow's disease). It will then review the knowledge of thyrotoxic crises as the most convenient method for the study of this disease. Finally, it will attempt the interpretation of the biologic pathogenesis of thyrotoxicosis.

Routine experiences with thyrotoxicosis include the following.

1. The usual type in which there is a gradual development of the disease to its maximum and in which the onset is not acute and does not apparently follow some well-defined incident or event. No crisis-like incident occurs during the course of the illness.

2. Similar types as in Group 1, but in which the onset of the illness is relatively acute and well marked owing to the fact that the disease follows some well-defined incident or event. No crisis-like incident disturbs the course of the illness.

3. A small group in which the illness follows some well-defined incident or event including mental shock, physical injury, etc. The progress of the disease is very rapid so that a fully developed clinical picture is very quickly established. Many of these patients develop extreme grades of exophthalmos. The initial phase of the illness resembles a crisis-like incident.

In one case, encountered many years ago, a woman in her twenties received a sudden great shock. Extreme nervousness occurred immediately, followed by tachycardia, sweating, diarrhea, loss of weight, and exophthalmos. Within a space of days there was a fully developed picture of exophthalmic goiter and the patient went through a typical crisis. She had been in a highly toxic state for more than one year before she was admitted to the hospital. She showed photographs of herself both prior to the beginning of the illness and later, and one could not help being powerfully disturbed at the change from a beautiful, slim girl, with a bright intelligent face, to a gross, fat, drab, old-looking woman, with a high grade of exophthalmos, and with a dull, unintelligent face which was almost repulsive.

4. A group of cases similar to those in Groups 1 and 2, in which for no discoverable cause, and/or with or without some mental or physical provocation, the toxic state of the patient becomes so markedly and comparatively suddenly increased that the patient passes into a crisis from which recovery does not often follow.

5. A group of thyroidectomies including those done in one or in multiple stages, or patients in whom some relatively trivial operation is done such as polar ligation. In these, following immediately after operation, the patient passes into a crisis. So many of the patients die that this constitutes the greater number of fatalities after operation. While this experience occurs in individuals with a preoperative state of high toxicity, I have seen instances in which the toxicity has been of moderate grade.

The postoperative crises are not necessarily limited to operations upon the thyroid. They are known to occur after other classes of operations and among these, rhinologic procedures possibly take a prominent place.

Cases of allergic rhinitis are relatively common in association with thyrotoxicosis. Flare-ups and crisis-like episodes are especially common after thyroid operations.

6. All of these groups are represented, possibly to a lesser degree, in postoperative recurrences.

7. Cases, sometimes of mild degree, in which following the use of iodine (Lugol's solution), similar exacerbations, even to the intensity of a crisis, occur.

8. Patients with marked mental aberrations and psychologic disturbances in whom thyroid operations are never known to relieve the mental disturbance.

To illustrate, there was one young married woman in whom a severe type of thyrotoxicosis was associated with mental symptoms centered chiefly in an uncontrollable desire to empty the bladder at the most unexpected and inopportune times, so that many times she involuntarily emptied her bladder under conditions which caused much embarrassment. After subtotal thyroidectomy, all of the previous symptoms disappeared except this one which could never be eradicated (six years' follow-up).

The Thyroid Crisis.—

Crises occurring in toxic thyroid disease may develop in any case, including the most unexpected. That thirty-three of forty-nine non-surgical deaths were due to crisis, as compared with twenty-three of the forty surgical deaths (Boyce⁹) is undoubtedly significant. Most of the nonsurgical deaths from crisis occur in the medical wards, in patients for whom surgery does not seem to have been contemplated.

Patients with toxic thyroid literally stand in jeopardy every hour. This condition is at its maximum immediately after thyroid operations. Patients in which there was no operation are subject to many other stimuli sufficient to throw them into a crisis. The subjects seem not to tolerate the mere act of living. They react badly to psychic trauma and to consequent emotional disturbances. The most trivial intercurrent illness or accident is enough to destroy their delicate balance and to throw them into crises which may readily prove fatal. Similar crises may also result from operations on distant organs and even minor surgical inter-

ventions, roentgen therapy (Bausi'), massive thyroid medication, and sudden interruption of a preoperative iodine therapy, infections, diagnostic procedures such as the determination of the basal metabolism, bodily exertion, and severe emotional strains. A severe thyrotoxicosis may also lead spontaneously to a crisis.

All thyroid types of operations—unilateral or bilateral resections of the gland, polar ligations, etc., either in single or multiple stages—carry the danger of a subsequent crisis in almost equal degree. For all surgeons, the relative number of such postoperative crises is to a certain extent a matter of skillful operative technique, of good fortune, and of good and prolonged preparation of the patient before operation. The latter, especially, is a most important factor.

At one of our hospitals I compared the results of operation and the frequency of occurrence of postoperative crises of the operations done in one stage by myself and those done by the other members of the staff who did their operations in multiple stages. I could not see much of any difference in results between the two groups.

The symptoms of the fatal postoperative crisis are characteristic and too well known to require description. Those of the other, the non-postoperative form, very similarly as the different clinical forms of thyrotoxicosis. Aggravation of existing symptoms is characteristic and those referable to some organic system, such as the gastrointestinal and cerebral systems, predominate.

In severe cases, the patient exhibits increasing muscular atrophy, frequent vomiting, diarrhea which defies treatment, motor unrest, anxiety, sleeplessness, psychotic delusions, and finally coma. There is dryness of the hair and skin. There is a tendency toward descending infection in the respiratory tract, and an increasing malfunction of the cardiovascular system. An increasing amount of urobilinogen is found in the urine with a tendency toward oliguria, and a great increase in creatine in proportion to the total creatinine.

The course of the illness during a crisis may be fatal after one or a few days, or the symptoms may recede after the exciting factor, such as infection, subsides or effective therapy is instituted.

No diagnostic means exists for detecting the impending crisis except in the clinical manifestations of the disease. Not always are these recognizable even to an observant physician. For this reason, every case deserves the utmost care and watchfulness.

1. *Pathogenesis, Pluriglandular Origin.*—Originally it was generally assumed that thyrotoxicosis was essentially a primary disorder of the thyroid. The possibility of the existence of varieties of thyrotoxicosis, in which the primary seat of the disease is outside of the thyroid, has since been recognized, however. Most clinical and research observers have classified the disease according to the assumed probable primary seat of the disorder as follows:

A. Primary. thyrotoxicosis, that is, thyrotoxicosis primarily of thyroid origin.

B. Secondary thyrotoxicosis, of which three subvarieties may be recognized:

- (a) Those of pituitary origin—thyrotropic hormone excess
- (b) Those due to deficiency or antithyrotropic principle
- (c) Those of endocrine origin other than pituitary.

The normal activity of the thyroid is dependent upon pituitary secretion. Experimental ablation or destruction of the pituitary gland leads to physiologic and morphologic involution and atrophy of the thyroid.

In many of the cases of crises, post-mortem examination has demonstrated the presence of changes in the posterior lobe of the pituitary (Sunder-Plassmann⁵⁴).

The pace-making thyrotropic factor is derived from the pituitary gland, but the demonstration of an excessive thyrotropic factor in the blood in thyrotoxicosis has so far been unsuccessful, possibly because the secretion is fixed or altered in some way to make it unrecoverable. The culminating factor in thyrotoxicosis is some degree of thyroid hyperactivity.

2. *Central Nervous System.*—In a number of cases, morphologic changes in the central nervous system have been observed, particularly in the hypothalamic centers; furthermore, hemorrhagic foci were found in the region of the vagal nucleus. In such cases, the entire brain shows marked changes reminding the pathologist of encephalitis.

There is a neurogenic conception of the etiology of the disease (Sunder-Plassmann⁵⁴). A neurologic connection to the thyroid has been established by the discovery in the thyroid of a neurohormonal cellular system connected through the parasympathetic system with the vascular endothelium and the thyrocytes of the follicles. These neurohormonal cells are distributed throughout the parasympathetic system and the endocrine glands; they form an independent parenchyma within the thyroid, and they determine the normal and abnormal output of the thyroid. The significant factor in exophthalmic goiter is the unrestrained absorption of both the stored and newly secreted colloid material.

Crises occurring spontaneously during conservative treatment show an extreme upset of the sympathetic nervous system and are caused by the unrestricted absorption by the neurohormonal cells and in the immediate postoperative period by thyroidectomy.

There is abundant clinical evidence (Marañón,³⁷ Étienne and Richard,¹⁸ Merklen,⁴⁰ Railliet,⁴⁷ Kahane,²⁷ Rothackers,⁴⁸ Johnson,²⁶ Bär,² and Dannehl,¹⁵) that an enormous number of cases of Graves' syndrome arose as the result of fear during World War I. Crile¹³ expressed the opinion that the characteristic facies and most of the symptoms of the patient with Graves' syndrome and those in man or in an animal in a state of fear are remarkably alike. As long ago as 1899, Darwin and Sir Charles Bell noted the marked neurogenic manifestations in toxic

patients of any sudden stimulation such as grief or anger, or other violent excitatory cause.

The heart beats quickly and violently so that it palpates or knocks against the ribs; there is trembling of all the muscles of the body; the eyes start forward and the uncovered and protruding eyeballs are fixed on the subject of terror; the skin breaks into a cold and clammy sweat, and the face and neck are flushed or pallid; the intestines are affected.

The phenomena of fear as thus indicated has many resemblances to the phenomena of an epileptic attack and convulsion. The close relationship of epilepsy and exophthalmic goiter was seen and commented upon by Patman.⁴⁷ Other observers remarked that each of these conditions had the same specific symptoms.

Apparently the nervous component of thyrotoxicosis is unrelieved by treatment (medical, thyroidectomy, etc.), possibly because the nervous pathways have become too firmly established and too responsive. In some cases these residuals represent a true psychoneurosis. The differentiation between toxic residuals and psychoneurosis is of prognostic significance. Follow-up studies show that there is a comparatively heavy incidence of nervous disorders after thyroidectomy, which would indicate that the operation removes only the most important glandular component and leaves the fundamental disorder untouched.

Diaz and Lorente⁴⁸ observed that the patients with exophthalmic goiter and with migraine eliminated during their crisis a substance with an intense acetylcholine effect, and they direct attention to the role of acetylcholine in the excitation of the sympathetic nervous system.

DISCUSSION

If one analyzes this factual knowledge, one is impressed by the following groups of clinical manifestations:

1. The frequent familiar constitutional tendency (Charcot,¹¹ Sattler,⁵⁰ Bauer,⁵ Ostwald,⁴² Püssler,⁴⁵ Holst,²⁵ Barker,⁷ Falta,¹⁹ Biedl,⁶ and Buschan¹⁰). Most clinicians have noted its occasional occurrence in two or more members of the same family (Sattler,⁵⁰ Buschan,¹⁰ Lerrede and Drouet,³³ Moss,⁴¹ Bauer,⁵ Chvostek,¹² Falta,¹⁹ and numerous others). Less frequently, Graves' disease has been reported as occurring in mother and child (Sattler,⁵⁰ Bauer,⁵ Lenz³²).

A case is described in which a hysterical woman had ten children, eight of whom had exophthalmic goiter. One of the children had four grandchildren, three of whom had exophthalmic goiter and one of these was also hysterical.⁴⁹

Souques and Lermoyez⁵³ saw sixteen such instances in adult members of one family during the course of three generations.

2. The onset of the illness is commonly referred to some well-defined incident or episode which is so recognizable to the patient that he very often voluntarily gives this information. In the exceptions, it is highly

probable that some such incident did occur, but, for some reason, most probably its insignificant or insidious character, it was not registered in the patient's mind.

The fact that the disease might originate very acutely and progress with great rapidity only emphasizes this point all the more. The characteristics of the nonoperative crises are very similar to the original manifestations at the time of onset of the total illness. In the postoperative cases, the evidence is overwhelming and is universally accepted, that the crisis is precipitated by the operation on the thyroid. The fact that crises may be originated after other types of operation, or after the many trivial and important causes previously referred to in this communication, indicates that in every case there has occurred a definite event which has preceded the crisis.

The fact that in the nonoperative crises there are examples in which no definite cause can be demonstrated does not alter the preceding statement necessarily. It means, perhaps, that the cause has been too trivial to register, as a single incident, but that it has been repeated many times; that in the discomforts of the illness, the patient did not appreciate or perceive the provocative cause; or that the powers of observation of the physician have not been sufficient to expose these causes, or that he was not available when they occurred.

3. In recurrent or persistent thyrotoxicosis, both in medically and surgically treated patients, the same factors and causes, including physical and psychic trauma, pregnancy, infections, etc., are always responsible for the exacerbation, recurrence, or persistence of the toxic state. The acuteness and severity of these manifestations vary as in the original stage of the disease and are of similar pattern. It is important to remember that this type occurs without, as well as after, operation.

4. No method of treatment, medical or surgical, actually "cures" the patient. No evidence exists that iodine, x-ray, or operation is curative, as the physician would know if he followed his supposedly cured patients until the end of their lives. Iodine brings about remissions of toxicity. It prevents aggravated manifestations of toxicity over long periods of time. It mitigates the severity of exacerbations which occur in the natural course of the disease. Anatomically, it produces involutionary changes in the gland. But by the same token, no gland is ever brought back by iodine to an entirely normal state, and clinically no toxic patient can ever be permanently cured by it. The stimulus to disease remains; sooner or later the gland returns to activity, and the toxicity flares up anew, as soon as iodine is withheld.

Anatomically, the following changes occur:

The first stage is that of hyperplasia, well recognized by the accompanying general symptomatology, including the thrill and bruit over the thyroid area. It is the stage of toxicity of hypervascularization.

The second stage is that of the so-called "resting" thyroid in which there is a tremendous accumulation of colloid within the acini. Con-

comitantly, the metabolic rate drops markedly toward or into the normal or minus rating, the weight increases, and there is a reduction of the heart rate to a satisfactory figure. But the exophthalmos may be unaltered or only slightly improved and in a certain percentage of instances (marked by a tendency toward excess weight) a little more prominent.

In the third stage thyroid involution occurs and in some cases atrophy actually occurs.

After operation, it appears as if the course and development of the disease has been cut off and stopped at the stage and time of the performance of the operation. The basal metabolism decreases more rapidly when subtotal thyroidectomy is performed than after medical treatment, because the thyroid gland is responsible for 40 per cent of the body heat (Dubois¹⁷). The patient gains weight, the pulse rate drops, and the tremor subsides to a degree. But, nevertheless, in spite of the fact that the patient states that he is "well," physical examination of the patient discloses that all of the previously existing objective symptoms and elicitable signs and manifestations are still present, including among others, the cardinal symptoms of thyrotoxicosis or exophthalmic goiter—nervousness or elicitable nervous symptoms and manifestations, rapid pulse exophthalmos, etc.

5. The secondary manifestations (complications of thyrotoxic disease including congestive heart failure, nitrogen retention, vomiting, diarrhea, rapid weight loss, emotional instability, an abnormally low index of respiratory stability (Bartlett¹⁴), an abnormally low liver function (Quick¹⁶), and an unsatisfactory exercise test (Bartlett¹⁴) are only temporarily, incompletely and sometimes not at all relieved, and are constantly subject to recurrences and exacerbations, so that the patient must be under constant medical surveillance.

In post-mortem room experiences, one is confronted with the following findings:

The Thymus.—In many cases a large thymus is found. It was found in from about 80 to 90 per cent of the fatal cases of Graves' disease by Seelig;¹² and Haberer⁵⁷ found a large thymus in 100 per cent of those patients dying from operation. Koehler²⁰ found an enlarged thymus in about 50 per cent and Hammer²³ in about 63 per cent of all patients with Graves' syndrome.

The first report of the association of a hypertrophied thymus with thyroid disease was made by Markham³⁸ in 1858. Numerous reports confirming his observations are in the literature (Matti,³⁹ MacKenzie,³⁴ Blackford and Freligh,⁷ Crotti,¹⁴ Giordano,²¹ Potter,⁵⁸ and Margolis³⁶). Blackford and Freligh,⁷ in a study of 117 necropsies on patients who had had thyroid disease, found hypertrophy of the thymus in every patient under 40 years of age with a hyperplastic gland and in every patient under 30 years of age with a nonhyperplastic gland. They considered thymic hypertrophy and lymphoid hyperplasia a result rather than a contributing factor to the thyrotoxicosis. Margolis,³⁶ in a more

recent post-mortem study of eighty-five cases of thyroid disease, observed hyperplasia of the thymus gland in 85 per cent of the patients with exophthalmic goiter and in 53 per cent of the patients with adenomatous goiter. He thought that the possible significance of the hyperplasia may represent a constitutional, inherent disposition to the development of hyperthyroidism.

The rapid development of the thyroid crisis and the frequent, often sudden, death of the patient have led to the belief that the complication may be associated in some way with a dysfunction of the thymus. Thymic death, however, does not resemble in many respects death from thyroid crisis, but the majority of patients dying in crisis are found, at autopsy, to have a persistent and hypertrophied thymus.

The muscular weakness manifesting itself in patients with Basedow's disease as well as the adynamia, which, in coma, finally develops into myasthenia, is regarded as the effect of the thyroid hormone upon the chemical metabolism of the musculature. In numerous casuistic observations, the coincidence of thymic enlargement and myasthenic symptoms has been noted.

That Graves' syndrome and thymic enlargement are not simultaneous reactions to the same insult is shown by the frequency with which they are totally dissociated in the same patient. It is well known that persons with the thymic constitution are extraordinarily sensitive, not only to physical influences such as traumatism, narcosis, infections, etc., but also to psychic influences. The latter is proved by the frequency of suicides and of neuroses among such patients (Koliski,³⁰ and Parata-schew⁴⁴). As the essential characteristic of the constitution of Graves' syndrome is the extraordinary sensitivity to physical and psychic stimuli, is it not reasonable to assume that the thymic constitution is merely a potential basis, not necessarily universal, for the development of Graves' syndrome?

The Liver.—In the cases reported by Foss, Hunt, and McMillan,²⁰ there was only one normal liver in the patients dying during true crisis. Ten of the eleven subjects showed varying degrees of necrosis in the center of the lobules. There were eight necropsies in which fatty degeneration of the liver cells was a prominent feature. This change was more marked in the livers in which necrosis was extensive. Cellular infiltration was present in three organs and congestion in one, the latter occurring in a patient who had healed mitral endocarditis.

The liver changes are remarkable. In the liver the action apparently starts at the periphery of the lobule and produces a parenchymatous degeneration of the cells similar to that produced by other toxic agents. There is a marked reduction in fat and an almost complete absence of glycogen, factors which probably preceded the degenerative changes. The fibrosis probably indicates a preceding condition of hepatitis, that is, hyperemia, edema, and degeneration without lymphocytic or leucocytic reaction.

Two types of liver parenchymal cells are responsible for the varied hepatic functions. The reticuloendothelial Kupffer cells clear the hepatic blood of particulate matter and share in the formation of antibodies and antitoxins. Each hepatic cell is a unit in itself, contributing its share to the multifold functions attributed to the liver as an organ.

In order to produce experimental hyperthyroidism, Seizky⁵¹ used thyroxin by hypodermic injection. The anatomic findings resemble those seen in acute and chronic clinical cases which have come to autopsy. The findings consisted of loss of weight and visceral changes in the liver, heart, kidneys, spleen, hypophysis, parathyroids, and pancreas. In the heart and liver, they were characterized by a richly vascularized fibrosis. In clinical medicine, liver changes are found in all cases of thyrotoxicosis and form an important part of the total illness (see Discussion).

The pancreas of the guinea pigs presented remarkable modifications. In the acute intoxication, there was degeneration amounting almost to necrosis of the islets. In the chronic intoxication, there was hypertrophy of the insular apparatus amounting to two or three times that found in the normal. The application of these experimental facts may indicate that the thyroid hormone stimulates pancreatic hyperplasia, which in turn empties the liver of its reserves.

The incorporation of the function of antibody activity and the protection against disease in the many and various physiologic activities of the liver are well known. In cellular destruction of the liver parenchyma, all functions are lessened and deteriorated. In thyrotoxic disease, it is well known that the liver abnormality is a most important factor.

Maddock and his associates⁵⁵ conclude that (1) preoperative studies of the hepatic function give no indication of the mildness or severity of the postoperative course, and (2) in the postoperative period there is an increase in the impairment of the hepatic function, with an increase in hyperthyroid reactions, but no evidence to show that one is the cause of the other. Lesions in the liver appear to be an integral part of the syndrome of severe toxic goiter.

Comparison With Certain Factual Knowledge of Allergic Conditions.

—Recent research has indicated that certain relatively obscure diseases may be dependent upon an increased reactivity of tissue to various known and obscure antigenic substances. Allergic responses occur in a large number of diverse conditions, can be demonstrated by skin reactions which are specific for some only, and are probably caused by some cellular protein substance or by other products of cellular metabolism. Frequently the reaction is a nonspecific one.

Weil⁵⁶ believes that anaphylactic and allergic reactions are of a cellular and not a humoral character, because he was unable to demonstrate the presence of any antigenic substance in the blood of experimental animals. He is convinced that the site of the reaction is in the paren-

chymal cells of the liver. In his experimental animals, Weil found that the liver dominates the entire picture: in the very severe cases, the organ is tremendously enlarged; it is intensely cyanotic and bleeds freely on section; the parenchymal cells show varying degrees of congestion and hemorrhage, clouding, swelling, and in severe cases, a disseminated necrosis.

In long-standing cases, the liver changes are even more marked and assume a chronic character even to certain fibrotic changes. Changes in the other organs are very similar to those described by Sciaky⁵¹ (see Discussion).

Neurologic Allergy.—The association of asthma, urticaria, migraine, and epilepsy has long been known. According to Blanton⁸ and to Kennedy,²⁸ the brain, meninges, and nerve trunks are all subject to the allergic reaction, characterized by vascular spasm and dilatation, sudden localized edema, and cellular infiltration (focal angioneurotic edema), and reflecting the location and degree of focal injury. According to Kennedy,²⁸ such focal areas (1) involving the brain substance cause epilepsy; (2) involving the meninges with painful stretching cause migraine; (3) involving nerve roots and trunks cause evanescent peripheral motor paralysis, and (4) that many cases of "transient palsies," retrobulbar neuritis, and maladies of peripheral nerves and spinal roots are all due to protein sensitization.

Changes in the brain during a migrainous attack were actually observed by Goltman²² in a patient with a cerebral decompression. In the initial stage the patient's face was pale and the area of decompression sunken (vasomotor spasm). With the appearance of headache and vomiting the face became suffused and through the decompression opening a bulging mass appeared (vascular dilatation and edema).

SUMMARY AND CONCLUSIONS

One must accept Hertzler's²⁴ conception of all thyroid disease as one continuous disease process. One must then arrive at the conclusion that some underlying condition is present, that the patients have been suffering from latent if not active toxicity for very long periods of time, and that all the manifestations, including all exacerbations and recurrences, are episodes of a single disease.

Very acute onsets, and all sudden exacerbations including all crises are due to the sudden release of some factor which acts in a very powerful manner, apparently through the thyroid, as an antigenic and/or catalytic agent in an already sensitized individual.

Thyroid operation in thyrotoxicosis followed by a thyroid crisis represents a laboratory experiment in which a successful "take" has occurred. The large number of "takes" only emphasizes this fact. The difficulty in understanding this sequence of events is due to the fact that the pathogenesis of this sequence is rarely made clear by post-mortem examination. In this state it is obvious that there are profound toxemia

and a violent and overwhelming disturbance of metabolic processes with, no doubt, a profoundly altered blood chemistry. Studies on the blood chemical variations in a state of crisis have not yielded satisfactory results, because the causal body has not yet been identified and cannot, therefore, be measured.

There is no doubt that the study and understanding of thyrotoxic crises furnishes the best approach and clue to the understanding of thyrotoxicosis in general.

Neurologic pathways and a neurohormonal cellular system have been demonstrated (Sunder-Plassmann⁴) whereby an excitatory cause could be quickly distributed and could bring about the acute and hyperacute onsets, and the equally acute exacerbations and crises. There is further factual knowledge regarding many similarities between thyrotoxicosis, neurologic allergy, epilepsy, and certain mental states, especially fear.

After the disease has been present for some time, the demonstrable pathologic-anatomic changes in thyrotoxicosis (Basedow's disease, exophthalmic goiter) are very similar to those seen in equally long-standing cases of allergic disease. In this regard the liver changes are especially important, and the knowledge of this anatomic and clinical association is well spread by this time. Because of inherent physiologic functions of the liver, this has special reference to sensitization and antibody formation.

This factual, clinical, and pathologic evidence seems overwhelmingly in favor of the viewpoint that thyrotoxicosis must be classified—at least as far as its pathogenetic mechanism is concerned—with the allergic group of diseases.

In the medical treatment of thyrotoxicosis and in the preparation of thyrotoxic patients for operation, iodine (Lugol's solution) seems to exert its beneficial effect by decreasing the sensitization of the patient. The occasional uncontrolled effect which it sometimes causes is in line with the occasional similar action of other antigenic bodies.

REFERENCES

1. Bansi, H. W.: Thyrotoxic Crisis and Thyrotoxic Coma (Die thyreotoxische Krise, das thyreotoxische Koma), *Ergebn. d. inn. Med. u. Kinderh.* 56: 305, 1939.
2. Bär: *Klin. Monatsbl. f. Augenh.* 59: 105, 1917.
3. Barker, L. F.: Nervous and Mental Symptoms in Exophthalmic Goiter, *J. A. M. A.* 71: 327, 1918.
4. Bartlett, W.: *The Surgical Treatment of Goiter*, St. Louis, 1926, The C. V. Mosby Company.
5. Bauer: *Die konstitutionelle Disposition zu inneren Krankheiten*, Berlin, 1921, Julius Springer.
6. Biedl: *The Internal Secretory Organs*, New York, 1913, William Wood & Company.
7. Blackford, J. M., and Freligh, W. P.: The Thymus in Adults With Especial Reference to Goiter, *Collect. Papers Mayo Clin.* 8: 507-512, 1916.
8. Blanton, Wyndham B.: *Handbook of Allergy for Students and Practitioners*, Baltimore, 1942, Charles C Thomas, Publisher.
9. Boyce, F. F.: Toxic Thyroid Disease as a Surgeon Would Have the General Practitioner Conceive It, With a Special Note on the Liver Factor, *Mississippi Valley M. J.* 62: 2-13, 1940.

10. Buschan: Die Basedowische Krankheit, Leipzig and Vienna, 1894.
11. Charcot, quoted by Chvostek: Morbus Basedow und die Hyperthyreosen, Berlin, 1917.
12. Chvostek: Morbus Basedow und die Hyperthyreosen, Berlin, 1917, Julius Springer.
13. Crile: Am. J. M. Sc. 145: 28, 1913.
14. Crotti, Andre: 'Thyroid and Thymus, ed. 2, Philadelphia, 1922, Lea & Febiger, p. 750.
15. Dannehl: Deut. mil.-ärztl. Ztschr. 44: 44, 1915.
16. Diaz, C. J., and Lorente, L.: Investigations on Sympathetic Disorders, Rev. clín. españ. 7: 237, 1942.
17. Dubois: Basal Metabolism in Health and Disease, Philadelphia, 1927.
18. Étienne and Richard: Bull. et mém. Soc. méd. d. hôp. de Paris 41: 894, 1917.
19. Falta: Handbuch der inneren Medizin, vol. 4, second part, 1927.
20. Foss, H. L., Hunt, H. F., and McMillan, R. M.: The Pathogenesis of Crisis and Death in Hyperthyroidism. J. A. M. A. 113: 1090-1094, 1939.
21. Giordano, A. S.: The Frequency of Thymic Hyperplasia in Toxic and Non-toxic Goiters, J. Indiana M. A. 16: 362-366, 1923.
22. Goltman: Quoted from Blanton.^s
23. Hammer: Folio neuro-biol. 12: 209, 1922.
24. Hertzler, A. E.: Pathogenesis of Goiter Considered as One Continuous Disease Process, Arch. Surg. 16: 61, 1928.
25. Holst, J.: Pathogenesis of Exophthalmic Goiter, Acta chir. Scandinav., Suppl. 4, pp. 1-91, 1923-1924.
26. Johnson: Lancet 2: 920, 1916.
27. Kahane: Wien. klin. Wehnschr. 28: 148, 1915.
28. Kennedy: Quoted from Blanton.^s
29. Kocher: Arch. f. klin. Chir. 92: 677, 1910.
30. Koliski: Lehrbuch der gerichtliche Medizin, Berlin and Vienna, 1902.
31. Lahey, F. H.: Critical Thyroid States, Their Diagnosis and Treatment, S. Clin. North America 16: 1521, 1936.
32. Lenz: Arch. f. Rassen- u. Gesellsch.-Biol. 13: 1, 1918.
33. Lerrede and Drouet: Bull. Soc. franç. de dermat. et syph. 28: 142, 1921.
34. MacKenzie, H.: Exophthalmic Goiter, Lancet 2: 815-821, 1916.
35. Maddock, W. G., Pedersen, Svend, and Collier, F. A.: Studies on Blood Chemistry in Thyroid Crisis, J. A. M. A. 109: 2130, 1937.
36. Margolis, H. M.: Possible Significance of the Thymus Gland in the Syndrome of Hyperthyroidism, Ann. Int. Med. 4: 1112-1133, 1931.
37. Marañón, G.: Ann. de méd. 9: 81, 1921.
38. Markham: Affection of the Heart With Enlargement of the Thyroid and Thymus Glands and Prominence of the Eyes. Tr. Path. Soc. Lond. 9: 163-164, 1857-1858.
39. Matti, H.: Deutsche Ztschr. f. Chir. 116: 425, 1912; quoted by Frazier and Brown.
40. Merklen: Bull. et mém. Soc. méd. d. hôp. de Paris 41: 894, 1917.
41. Moss: N. York M. J. 99: 482, 1914.
42. Ostwald: München. med. Wehnschr. 27: 907, 1915.
43. Patman, J. J.: Quoted by Sajous, in Tice: Practise of Medicine.
44. Parataschew: Virchows Arch. f. path. Anat. 273: 134, 1929.
45. Püssler: Deutsche Ztschr. f. Nervenhe. 6: 210, 1895.
46. Quick, A. J.: Clinical Value of the Test for Hippuric Acid in Cases of Diseases of the Liver, Arch. Int. Med. 57: 544, 1936.
47. Railliet: Bull. et mém. Soc. méd. d. hôp. de Paris 42: 1151, 1918.
48. Rothackers: München. med. Wehnschr. 63: 99, 1916.
49. Sajous, C. E. deM., in Tice: Practice of Medicine.
50. Sattler: Die Basedowische Krankheit, Leipzig, 1910, Wilhelm Engelmann.
51. Sciaky, I.: Experimental Hyperthyroidism in Different Species of Animals.
52. Seelig: Interstate M. J. 20: 678, 1913.
53. Souques, A., and Lermoyez, J.: Rev. neurol. 35: 20, 1919.
54. Sunder-Plassmann, P.: Exophthalmic Goiter and Its Treatment, Deutsche med. Wehnschr. 67: 141, 1941.
55. Weil, R.: J. Immunol. 2: 469, 525, 1917.
56. Wilensky, A. O.: Occurrence, Distribution and Pathogenesis of So-Called Liver Death and/or the Hepatorenal Syndrome. Arch. Surg. 38: 625-691, 1939.
57. Haberer, quoted from Moschcowitz: The Nature of Graves' Disease, Arch. Int. Med. 46: 610-629, 1930.
58. Potter, E. B.: Persistent Thymus in Exophthalmic Goiter, Warthin Ann. Vol., pp. 205-220, 1927.

COTTON SUTURES IN SURGERY OF WARFARE

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MEADE and Ochsner,¹ in 1939, suggested that cotton thread would be a very satisfactory suture for employment in war injuries in the field. One of the early reports of the use of cotton in present-day field surgery came from a 750 bed field hospital, shortly after the conclusion of the Carolina maneuvers of 1941, and embodied an analysis of 124 clean, contaminated, and infected wounds wherein cotton had been employed. The results obtained thereby were in support of the contention of Meade and Ochsner heretofore stated.

The current report describes further experiences with cotton sutures during a period of duty in the Southwest Pacific Area. In some situations the type of surgery performed has been analogous to that of the ordinary station hospital, while at other times it has consisted principally of the care of battle casualties. The work has been performed in a variety of circumstances—sometimes in modern buildings, sometimes in tents or makeshift shelters, and oftentimes in situations where some contamination by insects was unavoidable.

Throughout this time the employment of cotton for sutures and ligatures has been in the nature of a routine procedure, although there have been some fairly constant exceptions. Stainless steel wire has been regarded as the suture of choice for the actual repair of tendons, although cotton has been used for hemostasis and for closure in such cases. Catgut has been employed regularly in rectal surgery and for the mucosal suture in operations upon the gastrointestinal tract. Heavy braided silk is preferred for through-and-through closure of the abdomen. With occasional further exceptions cotton has been employed routinely.

Only nonmercerized cotton has been used. Interrupted suture technique has generally been employed. Quilting cotton (No. 50), either single or double, has been the size most frequently selected. When a finer suture was adequate, No. 70 or No. 100 was used. Ligation of large arteries was accomplished with No. 16 cotton.

COTTON SUTURES IN SURGERY OTHER THAN ON BATTLE CASUALTIES

The series for which cotton sutures were used in surgery other than on battle casualties consists of 534 major and minor operations of all types in which cotton was the sole or predominant suture. A detailed analysis of the cases constituting this series is given in Table I.

Received for publication, June 5, 1944.

TABLE I

Appendectomy	174
Hernia, inguinal	53
Hernia, umbilical or epigastric	11
Cholecystectomy	2
Perforated peptic ulcer	2
Gangrene of epiploic appendix	1
Rupture of liver	1
Appendical abscess	1
Cecostomy	1
Sigmoid colostomy	2
Retroperitoneal tumor	2
Resection or repair of perforation of bowel	2
Release of small bowel obstruction	2
Closure of fecal fistula	1
Suprapubic cystostomy	5
Subtemporal decompression	1
Cranial burr holes	2
Aneurysm of superficial temporal artery	1
Mixed tumor of parotid gland	2
Thyroid adenoma	3
Thyroglossal duct cyst	1
Branchial cleft cyst	2
Tracheotomy	1
Excision of male breast	8
Hydrocele	2
Excision of small benign tumors, cysts, etc.	55
Saphenous ligation	22
Plastic revision of cicatrix	16
Primary closure of fresh laceration	46
Repair of lacerated tendon	15
Débridement of soft tissue wound	13
Débridement of compound fracture	31
Skull	7
Sacrum	1
Humerus	2
Radius and/or ulna	1
Carpals, metacarpals, and phalanges	9
Tibia and/or fibula	5
Tarsals and metatarsals	6
Amputation	10
Mid-thigh	1
Midleg	1
Digit	8
Open reduction and internal fixation, simple fracture	12
Mandible	1
Humerus	1
Radius and ulna	1
Femur	4
Tibia and fibula	3
Tarsals and metatarsals	1
Patella	1
Débridement of wound of joint without fracture	2
Osteoplasty	7
Excision of bursa	5
Removal of loose body from joint	6
Acromioclavicular separation	2
Excision of semilunar cartilage	9

In this series only four complications which bear any apparent relation to the type of suture material are known to have occurred. In each of three hernias, repair was followed by a persistent draining sinus for correction of which a subsequent operation was performed. In one case of peritonitis, evisceration occurred following layer closure of the abdomen with cotton sutures.

In enumerating these complications, due cognizance must be taken of the fact that our opportunities for prolonged clinical follow-up are infrequent and that other complications may have arisen of which we have no knowledge. That their incidence should be large, however, is unlikely, inasmuch as patients were ordinarily retained in the hospital until they were able to resume full duty status. We have seen occasional instances in which, some months after operation, a subcutaneous ligature could be palpated through the operative scar, in spite of the fact that only the finest sizes of cotton were used in such locations.

In addition to the series just presented, cotton has been used as a routine hemostatic ligature in minor contaminated operations such as incision and drainage of abscesses or excision of pilonidal sinuses. No hindrance to wound healing which could be attributed to cotton was observed.

COTTON SUTURES IN THE SURGERY OF BATTLE CASUALTIES

The war wounds comprising the series in which cotton sutures were used in the surgery of battle casualties are 237 in number. The average interval between injury and arrival at this hospital was three to four days. The majority of patients in this group underwent their initial major surgery at our hands, the notable exceptions being in wounds of the abdomen and chest. Gross contamination of wounds was the rule, and infection had often become established to the point of frank suppuration. Meade and Ochsner³ have expressed the belief that the most important use of nonabsorbable suture material is in grossly contaminated cases.

The usual operative procedure consisted of the following: Careful cleansing of the skin; saucerization of the wound or unroofing of long tunnels; excision of all devitalized tissue; relaxation of incisions of enveloping fascias; removal of fragments of bone, metal, blood clots, or other debris; irrigation with normal saline solution; introduction of a thin film of sulfanilamide; loose application of petrolatum gauze, followed, when possible, by incorporation in padded plaster casts. Cotton ligatures were employed routinely in these cases. We were fortunate in having been so situated that the patients remained under our care for periods sufficiently long to permit adequate observations of the nature of healing in most wounds.

A detailed analysis of the cases constituting this series is given in Table II.

It is of interest to add that in forty-five instances Thiersch grafts were subsequently performed upon wounds in this series. It was the invariable rule that healthy granulation tissue grew over and covered such cotton as was implanted in the wounds, with resultant smooth granulating surfaces which were altogether satisfactory for the application of grafts.

TABLE 11

Sigmoid colostomy		3
Release of small bowel obstruction		1
Subphrenic abscess		1
Perinephritic abscess		2
Intra-abdominal abscess		2
Suprapubic cystostomy		1
Traumatic arterial aneurysm		3
Axillary	1	
Brachial	1	
Radial	1	
Débridement of wound involving soft tissue only		111
Scalp and face	4	
Thorax	19	
Buttocks and sacrum	8	
Penis, scrotum, and perineum	6	
Arm	12	
Forearm	9	
Hand and fingers	6	
Thigh	27	
Leg	17	
Foot	3	
Débridement of compound fracture		86
Skull	7	
Facial bones (including mandible)	6	
Clavicle	1	
Scapula	2	
Humerus	9	
Radius and/or ulna	9	
Carpals, metacarpals, and phalanges	7	
Ribs	9	
Pelvic bones	3	
Femur	8	
Tibia and/or fibula	8	
Patella	5	
Tarsals, metatarsals, and phalanges	12	
Amputation		16
Arm	3	
Thigh	4	
Tarsometatarsal	1	
Carpal	2	
Digits	6	
Débridement of wound of joint without fracture		4
Open reduction and internal fixation of simple fracture		3
Radius and ulna	1	
Humerus	1	
Femur	1	
Débridement and drainage of osteomyelitis	4	
Ulna	1	
Clavicle	1	
Ileum	1	
Femur	1	

No untoward effect could be attributed either directly or indirectly to the use of cotton in any one of the 237 cases constituting this series.

SUMMARY

Cotton has been adopted as the preferred suture material for surgical use at a 750 bed hospital in the Southwest Pacific Area. With occasional exceptions it has been used routinely. The series reported upon comprises 534 major and minor operations other than upon battle casualties

and 237 operations upon battle casualties. The latter group in particular includes many cases in which the wounds were extensively contaminated or grossly infected at the time of initial operation.

CONCLUSION

Cotton suture material may be employed safely and with highly satisfactory results in the surgery of war wounds without regard either to their degree of contamination and infection or to the elapse of time between injury and the institution of definitive surgery.

REFERENCES

1. Meade, W. H., and Ochsner, A.: Spool Cotton as a Suture Material, *J. A. M. A.* **113**: 2230-2231, 1939.
2. Sparkman, R. S., and Williams, W. H.: The Employment of Cotton Suture Material in the Field, *SurGICAL* **11**: 698-702, 1942.
3. Meade, W. H., and Ochsner, A.: The Relative Value of Catgut, Silk, Linen, and Cotton as Suture Materials, *SurGICAL* **7**: 485-511, 1940.

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THE SURGICAL AND ANATOMIC SIGNIFICANCE OF THE MAMMILLARY TUBERCLE OF THE LAST THORACIC VERTEBRA

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IN THE course of observations made on the mounted skeletons in the laboratory of the department of anatomy of the College of Physicians and Surgeons at Columbia University, I noticed that the mammillary process of the twelfth thoracic vertebra greatly differs from that of all other vertebrae in its shape and relationship to the superior articular process. It was thought that the specific character of the mammillary process of the twelfth thoracic vertebra could be responsible for a comparative inaccessibility to the articulation between the eleventh and twelfth vertebral articular processes and, thus, account for the nonunion in this area, as observed occasionally after spine fusion operations by the method of Hibbs.

In reviewing the extensive literature on this subject, it was found that one of the difficulties encountered was the nomenclature of the smaller processes of the vertebra, when attempts are made by the authors to define homologous structures. It is necessary, therefore, to correlate the nomenclature used by other authors with the nomenclature used in this article.

The twelfth dorsal vertebra represents the last thoracic vertebra in the human spine. In other mammals the number of dorsal vertebrae varies greatly. It is usually more than twelve. In the anthropoid apes the usual number is thirteen.

THE MAMMILLARY TUBERCLE

The human twelfth dorsal vertebra consists of a body which is connected by two short pedicles with the superior and inferior articular processes situated posteriorly; two short transverse processes are placed laterally and behind the superior articular processes. The transverse processes of this vertebra differ greatly from the corresponding ones of the other vertebrae. They are shorter than the others and appear rudimentary. They show variations which are either symmetrical or asymmetrical. These variations may be comparable to the variations of the articular processes observed by Whitney, who found that the asymmetry of articular processes is of relatively frequent occurrence and is limited to the last two rib-bearing vertebrae, and that there might be a relation between these variations and exaggerated handedness associated with certain professions.

The transverse process of the twelfth dorsal vertebra presents three tubercles or smaller processes: the superior, the lateral, and the inferior or accessory. The corresponding nomenclature and homologies of the tubercles, as accepted by a number of anatomists, are shown in Table I.

TABLE I

COMPARATIVE TERMINOLOGY OF THE TRANSVERSE AND RELATED PROCESSES OF THE ELEVENTH AND TWELFTH DORSAL AND FIRST LUMBAR VERTEBRAE

ELEVENTH DORSAL	TWELFTH DORSAL	FIRST LUMBAR
Transverse process	Transverse process	Transverse process
(1) Mammillary tubercle or superior process (2) Lateral process (3) Inferior process	(1) Mammillary tubercle or superior process (2) Lateral process (3) Inferior process	(1) Mammillary tubercle, Owen's meta-physiis (2) Homolog. of transverse process of dorsal vertebra (3) Accessory process or Owen's ana-physiis (4) Costal process
Rib	Rib	

In the course of examination of specimens of human spines, it was noticed repeatedly that the mammillary or superior process of the twelfth dorsal vertebra is much longer and stouter than the corresponding process of the eleventh dorsal or first lumbar vertebra. It was also noticed that the mammillary process is absent on all dorsal vertebrae above the eleventh. An important relation was found between the mammillary process and the superior articular process. This relation was not found in the lumbar vertebrae and seemed to be confined to the twelfth dorsal vertebra only, although sometimes the eleventh dorsal showed a similar but very much less pronounced disposition. When the twelfth dorsal vertebra is examined from the side, the mammillary process is found behind the superior articular process with a deep depression separating the two processes. When observed from its posterior aspect, the mammillary process seems to conceal the superior articular process. A comparison with the eleventh dorsal vertebra shows that the mammillary process is considerably smaller and is placed farther back from the superior articular process. The first lumbar vertebra has a completely different relationship; the superior articular process and the mammillary process are in the same plane, the articular process seems to be in direct continuation with the mammillary process, and there is no intervening depression between them (Figs. 1A, 1B, and 1C). Figs. 2 and 3 represent lateral and posterior photographs of the twelfth dorsal vertebra.

The depression between the superior articular process and the mammillary process of the twelfth vertebra (Fig. 3) forms an angle which in this illustration equals about .67 degrees. The relation of the length of the superior articular process from the apex of the depression to the length of the mammillary tubercle from the apex of the depression is 28:23. The relation of the actual height of the superior articular process to the height of the mammillary tubercle is 25:27. This method

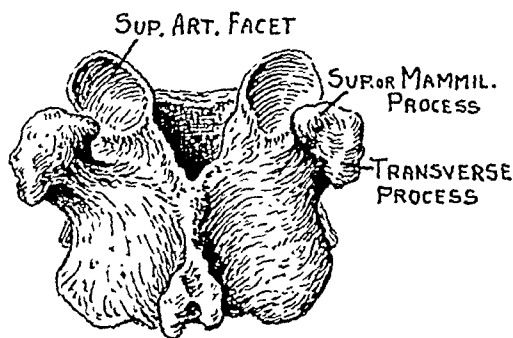
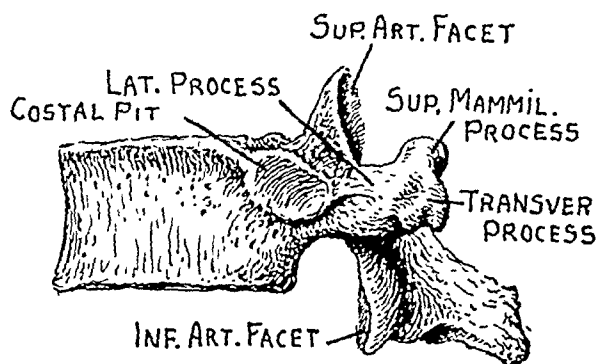


Fig. 14.—The human eleventh dorsal vertebra for comparison with Fig. 1B and Fig 1C.

of measurement, represented in Fig. 4, was applied to an analysis of the last two dorsal and first lumbar vertebrae in a series of white and Negro, male and female patients. The results of the measurement showed that the height of the mammillary process of the twelfth dorsal varied in relation to the height of the superior articular process but was almost invariably much higher than the mammillary process of the eleventh.

The angle between the superior articular and mammillary processes varied from 50 to 90 degrees. With the increase of the angle, the articular facet was found to be inclined more forward so that the cartilaginous surface of the facet was found to be directed more cephalad. The angles on the left and right sides were not always

symmetrical. In 43 per cent of the spines examined, the angle on the right side was greater. In 36 per cent it was found greater on the left side, and only in 21 per cent was it found symmetrical. The difference between the angles varied from 5 to 10 degrees and in one case reached 28 degrees. No great significance was attached to this variability. It may have the same significance as the variation of the articular processes as observed by Whitney and mentioned previously.

It is shown in Table II that although the mammillary tubercle of the eleventh vertebra may reach in certain instances less than one-half of the height of the superior articular process, in the majority of the examined spines, the height of the mammillary process of this vertebra

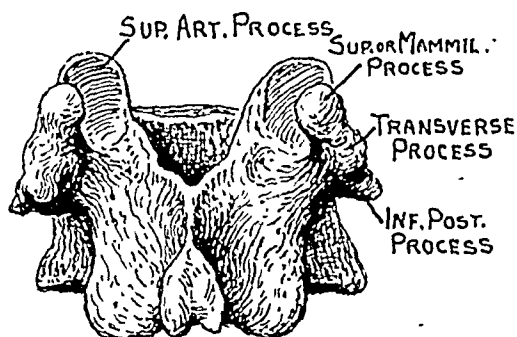
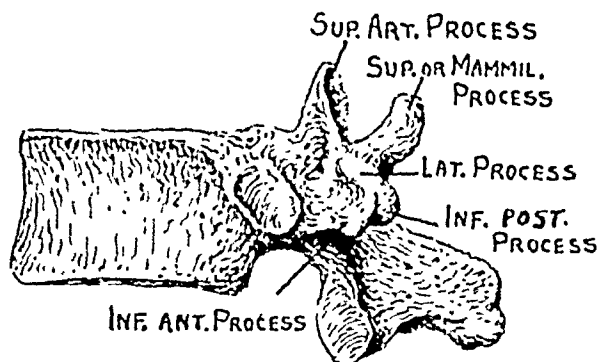


Fig. 1B.—Twelfth dorsal vertebra.

was almost insignificant in comparison with the height of the mammillary process of the twelfth vertebra. In one case the mammillary processes of the twelfth vertebra were of the type encountered on the eleventh vertebra, but in this case there was apparently an additional dorsal vertebra, because the first lumbar had all the characteristics of a dorsal vertebra. The mammillary process of the twelfth vertebra, in more than one-half of the examined spines, equaled more than one-half, or about one-half the height of the superior articular process.

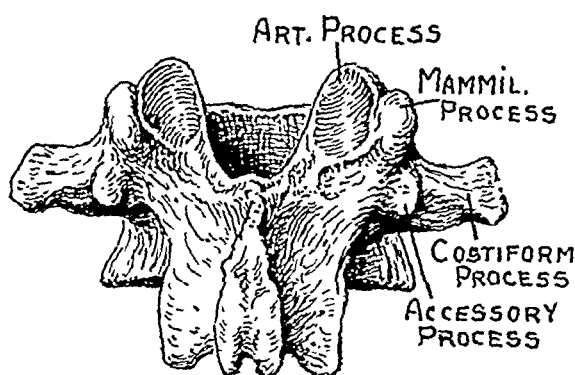
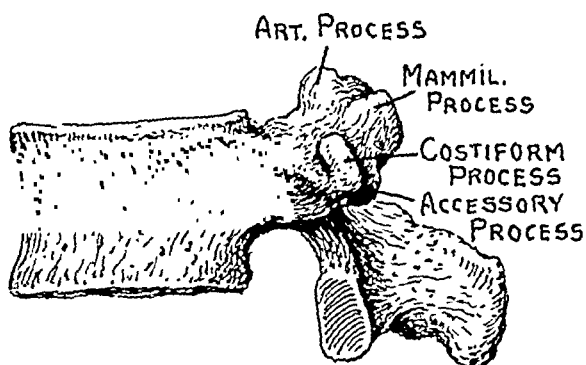


Fig. 1C.—The first lumbar vertebra.



Fig. 2.—Photograph of the posterior view of the twelfth human vertebra.

There was no visible mammillary process on the tenth dorsal vertebra and none above the tenth. The mammillary process of the lumbar vertebra, as mentioned before, lies lateral to the articular process and does not resemble in the least the typical relation between the two processes. The specific relation of the tubercle seen on the isolated twelfth vertebra was found more interesting on the mounted skeleton



Fig. 3.—Photograph of the lateral view of the twelfth human vertebra.

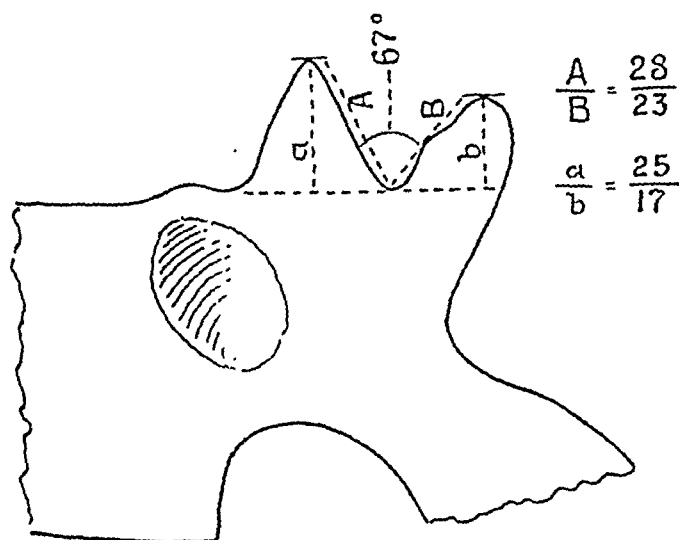


Fig. 4.—Method of measurement of the ratio between the height of the mammillary and superior articular process.

(Fig. 5). Here the mammillary process of the twelfth vertebra covered the joint between the inferior articular process of the eleventh vertebra with the superior articular process of the twelfth from behind, so that the joint itself was somewhat concealed. The joint between the inferior articular process and the superior articular process

between the ninth and tenth and the tenth and eleventh dorsal vertebrae, as well as that between the twelfth dorsal and first lumbar, can be seen very well from behind because it is not obstructed by the large mammillary tubercle, as seen almost constantly on the twelfth dorsal vertebra.



Fig. 5.—Photograph of the right side of a mounted skeleton. The articulation at the top of the illustration is between the tenth and ninth dorsal vertebra. The lowest articulation is between the twelfth dorsal and first lumbar.

The relation of the tubercle to the articular process on the mounted skeleton induced an x-ray study of the area on living subjects. A review of over one hundred x-ray pictures of the spine disclosed that the relationship of the mammillary processes of the vertebrae was not visualized in the ordinary film. If need be, a special technique will probably have to be devised for visualization of the mammillary tubercles.

TABLE II

RATIO OF ACTUAL HEIGHT OF THE MAMMILLARY PROCESS TO THE ACTUAL HEIGHT OF THE SUPERIOR ARTICULAR PROCESS OF THE VERTEBRAE

NO.	ELEVENTH DORSAL		TWELFTH DORSAL		FIRST LUMBAR		REMARKS
	LEFT	RIGHT	LEFT	RIGHT	LEFT	RIGHT	
1	.33	.40	.66	.90			
2	.50	.67	.83	.83			
3	.23	.45	.50	.62			
4	.10	.10	.45	.30			
5	.08	.07	.30	.10	.90	.62	The lumbar is a typical last thoracic
6	.07	.06	.36	.45			
7	.30	.20	.50	.33			
8	.01	.01	.30	.25			
9	.01	.09	.50	.50			
10	.20	.18	.33	.17			There is a deep depression between the processes on the twelfth
11	.20	.40	.50	.50			
12	.17	.33	.60	.50			
13	.17	.15	.55	.50			
14	.07	.14	.43		Lumbar type		
15	.01	.01	.70	.25			
16	.30	.20	.23	.65			
17	.01	.01	.50	.60			
18	.02	.02	.40	.43			
19	.02	.03	.48	.45			
20	.03	.04	.46	.44			
21	.06	.08	.60	.50			

It may be of interest to note that the mammillary processes of the last thoracic, lumbar, and sacral vertebrae have special epiphyses which appear about the time of puberty and join the rest of the vertebrae after the eighteenth year.

COMPARATIVE ANATOMY

A systematic and detailed study of the comparative anatomy of the vertebral column belonging to different animal groups is a very large subject presenting obvious difficulties. It is not within the scope of this article. This study was restricted to observations on a limited available material. Useful information was obtained from examination of casual specimens of quadrupeds and anthropoid apes, on exhibition specimens in the American Museum of Natural History and also from the literature. I was also able to examine the spines of twenty gibbons of an excellent collection belonging to Dr. S. Washburn of the department of anatomy of the College of Physicians and Surgeons.

As a result of this study it was found that the mammillary process exists in a number of animals. It may assume a variety of forms and occupy a variable position in relation to the articular process and lamina. Vallois made valuable observations on the spine of Cetacea. He noticed that the mammillary process, found in the cervical and anterior dorsal spine, is located on the base of the transverse process, behind the articular process. Further in the posterior dorsal region the mammillary process migrates along the vertebral laminae toward the spinous process and becomes a feature of the spinous process on the vertebrae of the lumbar region. It then loses all relation to the articular process. In most of the amphibians it is usually extremely small and

does not bear any direct relation to the articular processes. Flower and Gadow described a peculiar relationship of the superior articular process and the mammillary process in the great anteater (*Myrmecophaga jubata*). This animal has a double superior articular process in the lower dorsal region. Close observation shows a small mammillary process situated somewhat above and entirely laterally on the eleventh dorsal vertebra. There is also a very small mammillary process in the lumbar region of this animal. The mammillary processes are described in domestic animals. In the horse, with eighteen thoracic vertebrae, a mammillary process is described in the last four or five vertebrae. The processes are located laterally to the anterior articular process of the vertebra. In the cow, with thirteen dorsal vertebrae, the mammillary process is found to be quite small and rounded and located laterally to the anterior articular process. In the pig, with fourteen or fifteen dorsal vertebrae, a mammillary process is observed projecting laterally from the anterior articular process. In the dog, with thirteen dorsal vertebrae, the mammillary processes are observed on the last seven or eight dorsal vertebrae. They also project laterally to the anterior articular surface and are usually small.

Examination of three spines of gorillas, six of chimpanzees, and three of orangutans showed the presence of small mammillary processes on the last two thoracic and on the lumbar vertebrae. The mammillary processes of the dorsal vertebrae of the apes were very small and were situated laterally in relation to the articular superior process. The articulation between the eleventh and twelfth dorsal vertebrae was not covered by the mammillary process from behind as observed in the human spine. In general, in none of the examined animals did the mammillary process bear the same relation to the superior articular process of the twelfth vertebra as described in the human spine.

In the gibbon the mammillary process of the last two thoracic vertebrae showed a relationship to the superior articular process similar to that in the human being. The gibbon, as a rule, has thirteen dorsal vertebrae. The mammillary process of the last thoracic vertebra is located behind the superior articular process; there is a deep depression between the two processes and the joint between the twelfth inferior articular process and the thirteenth superior articular process is concealed by the mammillary process of the thirteenth thoracic vertebra in a manner similar to that found in the human being (Fig. 6). There is a great variability of the size of the mammillary process and a frequent transition of the larger mammillary process from the thirteenth to the one above or to the one below. Of the twenty gibbon spines examined, twelve showed the mammillary process on the thirteenth dorsal vertebra (last thoracic), six showed a shift to the twelfth dorsal (corresponding to the eleventh dorsal human vertebra), and two showed a typical lumbar structure.

Apparently the gibbon is the only animal with mammillary processes bearing a relationship to the superior or articular process similar to man. This fact may be of some importance since it is known that of all the mammals besides man, the gibbon is the only one which frequently assumes an orthograde biped position while running on the ground.

From the foregoing description it becomes apparent that: (1) the mammillary process is found universally in animals, (2) its position and size are variable in relation to the articular process, and (3) the existence of a large mammillary process of the twelfth human vertebra is similarly found only on the thirteenth (last thoracic) vertebra of the gibbon.



Fig. 6.—Comparative view of the eleventh and twelfth dorsal vertebra and first lumbar of a human specimen in the upper row. The eleventh, twelfth, and thirteenth dorsal and first lumbar of a gibbon specimen are shown in the lower row of this illustration.

The variability of the size and location of the mammillary process was investigated by Vallois, who established with a great degree of probability that in comparative anatomy the mammillary process is a migrating structure, occupying various places on the transverse process and laminae of the dorsal and lumbar vertebrae, according to functional demands and relative development of the transversospinal and longitudinal systems of the intrinsic dorsal muscles. The similarity of the mammillary process in man and the gibbon may suggest an interdependence between the two factors, mammillary process and orthograde biped position.

INTRINSIC MUSCLES OF THE SPINE

There are two groups of muscles which are of interest to us in the lower dorsal and upper lumbar region: the longitudinal consisting of a superficial and a deep layer, and the transversospinal consisting of three

layers. The longitudinal superficial system has three groups of muscles situated from the medial line outward in the following order: the spinalis dorsi, longissimus dorsi, and iliocostalis dorsi; the deep longitudinal group consists of the levatores costae in the dorsal region and of the intertransversarii system in the lumbar and dorsal region. The transversospinal group has three layers of which the most superficial is the semispinalis dorsi, the intermediate is represented by the multifidus, and the deep by the rotatores. It is important to review in brief the origin and insertions of all these muscles for further understanding of the significance of the mammillary process.

The Longitudinal Group.—The spinalis dorsi originates from the tips of the spinous processes of the first and second lumbar and twelfth and eleventh dorsal, and is inserted into the tips of the spinous processes of the first ten dorsal vertebrae. The longissimus dorsi has a common origin with the iliocostalis lumborum. About the level of the twelfth rib the separation of the two muscles becomes evident. The longissimus dorsi is inserted into the lower border, back of the accessory tubercles of the lumbar vertebrae, the lateral aspect of the mammillary process, and the inferior margin of the transverse processes of the thoracic vertebrae and the inferior margins of the ribs lateral to the costal tubercles. The iliocostalis dorsi coming up from the common mass takes additional origin from the superior border of the lower seven ribs, medial to the angles, and is inserted into the upper seven ribs near their angles and to the transverse process of the seventh cervical vertebra.

The Transversospinal Group.—The transversospinal muscles, difficult to dissect, and presenting multiple variations, are differently described by many authors. It seems that for clarity and simplicity, Trolard's description, as given by Testut, is perhaps the best. The semispinalis dorsi, the multifidus, and the rotatores all take origin from the medial side of the mammillary process and the corresponding upper border of the transverse processes according to the region involved. From this area of origin they divide into four different groups: (1) the spinous, directed toward the spinous process of the fourth vertebra above and corresponding to the semispinalis, (2) the subspinous, directed to the base of the spinous process of the third vertebra above and corresponding to the multifidus, (3) the long laminary, directed and inserted into the inferior border of the lamina of the second vertebra above and corresponding to the rotator longus, and (4) the short laminary, directed and inserted into the external aspect of the lamina of the first vertebra above and corresponding to the rotator brevis (see Fig. 7).

FUNCTIONAL SIGNIFICANCE OF THE MAMMILLARY PROCESS

A functional analysis of the spinal musculature in relation to motion of the trunk is a problem presenting many difficulties. When the area

under consideration is examined, two important factors stand out. The first is the generally accepted view that the line of gravity in the static orthograde position of the human spine passes through the body of the ninth dorsal vertebra or in its vicinity. The second factor is that the area of transition between the thoracic and lumbar vertebrae is associated with a functional transition of motion of the thoracic and lumbar spines. The thoracic spine is concerned mostly with torsion and lateral inclination, the lumbar spine with anteroposterior motion. The semispinalis and the multifidus, which originate from

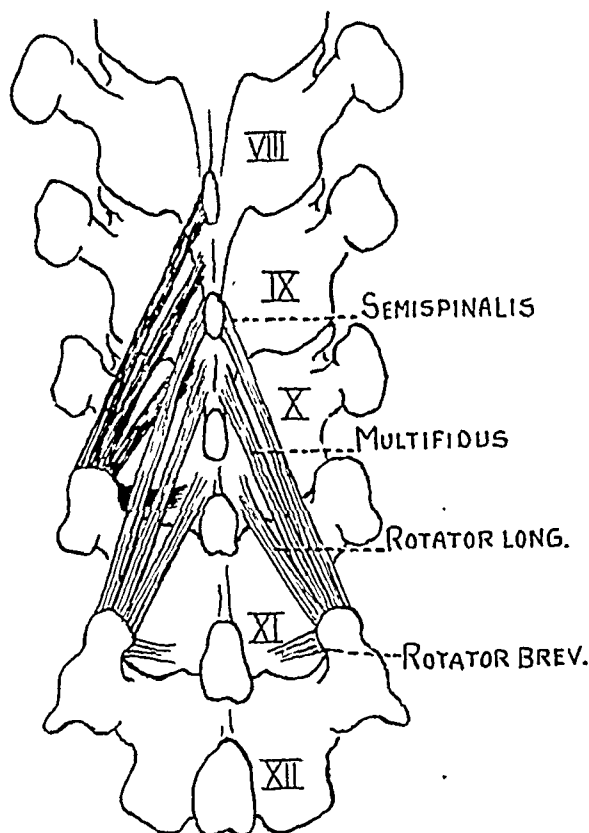


Fig. 7.—Schematic drawing of the intrinsic transversospinal muscles of the human dorsal spinal musculature after the description of Trolard.

the mammillary process of the twelfth vertebra, are inserted into the spinous process of the ninth and into the base of the tenth. Together with the rotator muscles they form a strong group which probably plays an important role in this area of functional transition. The size of the mammillary process of the twelfth vertebra is probably related to the functional demand upon the muscles originating from it.

THE SURGICAL SIGNIFICANCE OF THE MAMMILLARY PROCESS

The presence of a prominent mammillary process on the twelfth dorsal vertebra is important for two reasons. It may serve as a useful

landmark in the posterior surgical approach to the spine. When the spinous processes of the lower dorsal and upper lumbar vertebrae are exposed and further exposure of the laminae is obtained, it will be noticed, proceeding from the dorsal to the lumbar vertebrae, that the space between the spinous processes in the midline and the transverse processes laterally becomes narrower. Palpation of the lateral side of this space will reveal to the palpating finger a slight prominence corresponding to the mammillary process of the eleventh vertebra. Just

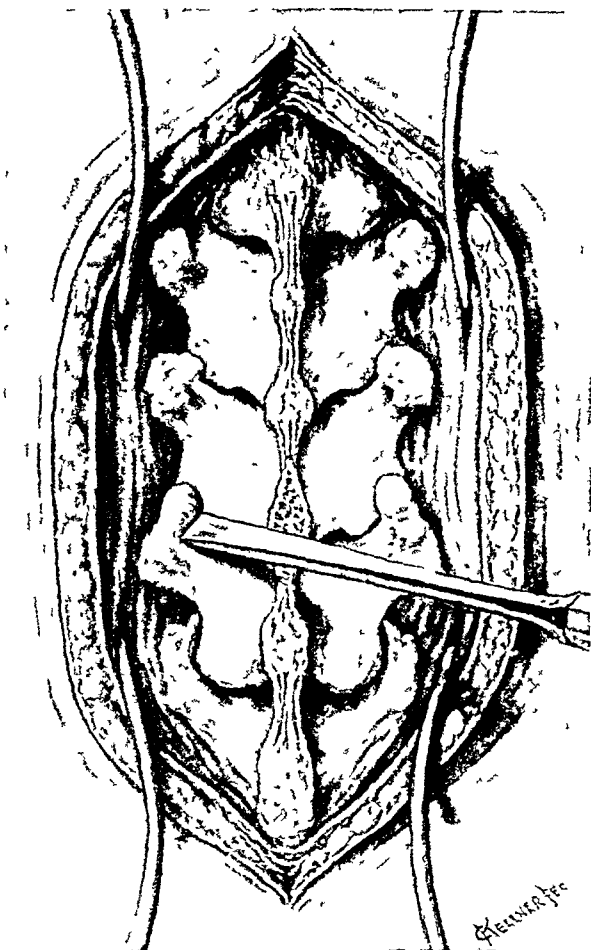


Fig. 8—Surgical exposure of the lower dorsal vertebra with resection of the mammillary process of the twelfth dorsal vertebra

below this a much larger prominence will be felt and this will correspond to the mammillary process of the twelfth vertebra, which in its turn will indicate the position of this vertebra.

Fig. 5 indicates clearly the second reason for the importance of the mammillary process. It conceals the articulation between the inferior articular facet of the eleventh and the superior articular facet of the twelfth dorsal vertebra from behind. Proper removal of the cartilage

of these facets in the fusion operation of the spine may be accomplished properly only after the removal of the mammillary process of the twelfth dorsal vertebra. This can be done after proper exposure, with a narrow osteotome, as shown in Fig. 8. It is believed that the omission of this operative step is responsible for occasional nonunion in this area, when an arthrodesis of the articular facets is performed.

SUMMARY

A study of the anatomic, functional, and surgical importance of the mammillary process of the twelfth dorsal vertebra was made. The process was found to be large and prominent on the twelfth dorsal vertebra. On the articulated spine it concealed the joint between the superior articular process of the twelfth and the inferior articular process of the eleventh dorsal vertebrae. A similar mammillary process was found on the last thoracic vertebra of the gibbon. The size and relation of the mammillary process were shown to present a good localization point for the twelfth dorsal vertebra in surgery of the spine. In spine fusion operations, involving the eleventh and twelfth dorsal vertebrae, a resection of the mammillary process of the twelfth vertebra is necessary for proper exposure of the joint between these two vertebrae.

I wish to express my gratitude to Dr. S. L. Washburn for valuable suggestions and the use of his excellent collection of gibbon skeletons, to Dr. H. Shapiro of the American Museum of Natural History, for placing at my disposal a collection of human skeletons, and also to the staff of the Department of Anatomy of the College of Physicians and Surgeons, for much appreciated help.

REFERENCES

1. Bardeen, C. R.: Development of the Skeleton and of the Connective Tissues in Manual of Human Embryology, Vol. I, Kiebel and Mall, Philadelphia, 1910, J. B. Lippincott Co., p. 353.
2. Cyriax, E. F.: On Certain Normal Irregularities of the Vertebral Column in Its Lower Dorsal Area, *Jour. Anat.* 56: 147, 1922.
3. Dawes, B.: The Development of the Vertebral Column in Mammals, *Phil. Tr. Royal Soc., London*, ser. B., p. 218, 1930.
4. Elftman, H.: Columbia University. Personal communication.
5. Ellenberger, W., and Baum, H.: *Handbuch der vergleichenden Anatomie der Haustiere*, Berlin, 1932, J. Springer, pp. 44-55.
6. Eycleshymer, A. C., and Schoemaker, D. M.: *Anatomical Names*, Baltimore, 1917, William Wood & Co., p. 115.
7. Flower, W. H.: *An Introduction to the Osteology of the Mammalia*, London, 1870, Macmillan Co., pp. 44-58.
8. Frazer, J. E.: *The Anatomy of the Human Skeleton*, ed. 3, London, 1933, J. & A. Churchill, p. 27.
9. Gadow, H. F.: *The Evolution of the Vertebral Column*, London, 1933, Cambridge University Press, pp. 55, 231.
10. Jamieson, E. B.: *Dixon's Manual of Human Osteology*, ed. 2, London, 1937, Oxford University Press, pp. 43, 47.
11. Kopsch, Fr.: Die Nomina Anatomica des Jahres 1895 (BNA), nach der Buchstabenreihe geordnet und gegenübergestellt den Nomina Anatomica des Jahres 1935 (I.N.A.), Leipzig, 1937, Georg Thieme.
12. Lanier, R. R., Jr.: The Presacral Vertebrae of American White and Negro Males, *Am. J. Phys. Anthropol.* 25: No. 3, 1939.
13. LeDouble, A. F.: *Traite des Variations des os de la Colonne Vertebrale*, *Gaz. méd. du centre*, Tours 12: 1-29, 1912.
14. MacBride, E. C.: Recent Work on the Development of the Vertebral Column, *Biol. Rev.*, (7), Cambridge, 1932.
15. Sappey, Ph. C.: *Traite d'Anatomie Descriptive*, Vol. I, ed. 4, Paris, 1888, p. 295.

16. Schultz, A. H.: The Relative Length of the Regions of the Spinal Column in Old World Primates, *Am. J. Phys. Anthropol.* 24: 1-22, 1938.
17. Steindler, A.: *Mechanics of Normal and Pathological Locomotion in Man*, Springfield, 1935, Charles C Thomas.
18. Struthen, J.: On the Articular Processes of the Vertebrae in the Gorilla Compared With Those in Man, *J. Anat.* 27: 131, 1892.
19. Terry, R. J.: In Morris' *Human Anatomy*, ed. 10, Philadelphia, 1942, The Blakiston Co.
20. Testut, L.: *Traite d'Anatomy Humaine*, Vol. I, ed. 8, Paris, 1928, G. Doin, pp. 61, 74, 902.
21. Vallois, H.: La Vertebre Diaphragmatique et la Separation des colonnes Dorsale et Lominaire chez les Mammiferes, *Compt. rend. Soc. de biol.* 85: 974, 1921.
22. Vallois, H.: La Signification des apophyses Mammillaires et Accessoires des Vertebres Lombaires, *Compt. rend. Soc. de biol.* 83: 113, 1920.
23. Weber, M.: *Die Saugetiere*, ed. 2, 1928. *The Primates*. Translation into Russian with addenda by M. F. Nesturkh, Gov. Publ. of Biol. & Med. Lit., Moscow Library, 1936, p. 203.
24. Whitney, C.: Asymmetry of Vertebral Processes and Facets, *Am. J. Phys. Anthropol.* 9: 451, 1926.
25. Wood Jones, F.: *Man's Place Among the Mammals*, London, 1929, F. Arnold.

TRAUMATIC OSTEOCHONDRITIS OF THE PATELLA

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WHEN a direct blow to the patella is received, the patella is driven against the adjacent femoral condyle and a greater or lesser degree of compressive force exerted upon the subchondral bone. This causes the development of areas of necrosis in the subchondral bone of the patella and femoral condyles which can be considered in almost the same light as a fracture. According to Bozan¹ the necrosis of bone may be attributed to the fact that the "minute girders of cancellous structure break at places predetermined by 'the laws of mechanics.' The broken mass of trabeculae interrupts the flow of blood and causes necrosis of certain predetermined segments." If the initiating trauma is mild and the amount of damage to subchondral bone minimal, spontaneous absorption and repair of the involved bone may occur. If, however, the area of necrosis in subchondral bone is more extensive, the area of involved bone is walled off and becomes a true sequestrum. Immediately, gross interference with the nutrition to the overlying articular cartilage layer develops, and consequent degenerative changes in that cartilage begin to appear. When these changes persist for a period of time, thinning of the articular cartilage of the patella, irregularities in contour, and fissures may occur. As a later manifestation, the synovium of the knee joint becomes irritated. In response to this irritation hypertrophy of the synovium and a chronic effusion result. Should the lesion remain untreated for a period of years, progressive arthritic changes in the knee joint will be found.

The lesion is certainly not uncommon. Darrach^{2, 3} states that the articular cartilage of the patella showed evidence of chondritis in 36 cases out of a series of 157 arthrotomies performed for internal derangement of the knee joint. Chaklin⁴ reported a series of 159 arthrotomies in 38 cases of which changes involving the articular cartilage of the patella and femoral condyle were discovered. Six examples of this condition have come to my attention.

REPORT OF CASES

CASE 1.—G. P., a white woman, aged 28 years, was admitted to Charity Hospital in New Orleans, Nov. 18, 1940, because of constant pain on weight-bearing for about eight weeks.

The patient had sustained an injury to the knee on three separate occasions, the first in 1928, the second a year later, and the last about two months before admission.

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Read at the meeting of the American Academy of Orthopedic Surgery, Chicago, Ill., January, 1943.

Received for publication, July 17, 1944.

She complained of some pain over the femoral condyles. Examination revealed slight effusion within the knee joint. Slight crepitation was elicited upon motion of the patella over the femoral condyles, but this motion did not produce pain. The most severe pain was felt when the examiner manually attempted to dislocate the patella laterally. There seemed to be a definite increase in the lateral mobility of the patella.

A diagnosis of recurrent dislocation of the patella and chronic synovitis was made. Nov. 20, 1940, the right knee was explored through a median parapatellar incision. When the joint was opened, a moderate amount of yellowish joint fluid escaped. Extensive synovial changes were apparent. There was definite synovial thickening and hypertrophy. The most striking changes were seen on the underside of the patella. Extensive fissures were present; there was widespread degeneration of cartilage and the process was diffuse.

Cross section of the entire patella showed an extensive area of fibrillary degeneration of the articular cartilage, the direction of which was at right angles to the articular surface. The cartilage showed longitudinal splits and wrinkles and the cartilage cells around these "fractures" had disappeared leaving an acellular matrix. Beneath this area the zone of intermediate calcification was absent and the subchondral area showed fragments of necrotic bone and cartilage present as loose masses filling the trabecular spaces. No definite line of infiltration of the subchondral plate could be seen in this section. This was probably due to the plane in which the section was cut. However, in every other respect the appearance was typical of osteochondritis.

While the patient was in the hospital a malignant breast tumor was discovered. Approximately one year later, she died from widespread pulmonary metastasis. During the interval when activity was possible, the knee gave no symptoms.

CASE 2.—A. T. T., a white man, aged 36 years, was admitted to Charity Hospital in New Orleans, July 3, 1941, complaining of pain on weight-bearing and a "snapping" or "locking" in the knee. He had been using crutches since sustaining an injury to his right knee about one year before when he fell off a hay wagon. The internal semilunar cartilage was removed at another hospital. He was unable to state whether or not the cartilage was damaged. The symptoms persisted following the operation. Examination revealed findings similar to those in Case 1.

A preoperative diagnosis of internal derangement of the right knee joint, probably a remnant of the internal semilunar cartilage, was made. July 9, 1941, through a median parapatellar incision the right joint was explored. The gross pathologic findings at operation were characteristic of this condition. The patella was completely excised, and the defect in the patellar tendon repaired with interrupted cotton sutures.

Aug. 8, 1941, the patient was ambulatory with motion in the right knee from an angle of 180 degrees in extension to 90 degrees in flexion. The "snapping" and "catching" sensations in the right knee had completely disappeared.

CASE 3.—D. M. V., a Negro woman, aged 21 years, came to Charity Hospital in New Orleans, Oct. 23, 1941, because of vague pain and swelling in the right knee and a sensation of occasional "catching of the knee."

Two years prior to entry, the patient struck her right knee forcibly against a washtub. There was no immediate disability, but within a week the knee became greatly swollen and extremely painful.

The patient walked without a limp. Palpation revealed slight thickening of the synovium. There was an increase in the amount of joint fluid, but no ballottement of the patella was possible. Complete flexion and extension of the knee could be accomplished, but slight pain was felt upon extremes of motion. Passively, motion of the patella was free, but there was a palpable grating sensation as the patella was moved over the femoral condyle, and some slight pain was produced. Circumferen-

tial measurements showed one-quarter inch atrophy in the right thigh. Laboratory findings were negative. Roentgenograms showed slight atrophy of the injured patella as compared with the normal side. On the lateral view there appeared a slight area of decreased density on the lateral femoral condyle which shaded into normal density at the periphery. No significant changes could be made out in the contour of the patella itself.

A preoperative diagnosis of chronic synovitis of the right knee of unknown etiology was made. Nov. 5, 1941, the knee joint was opened through a median parapatellar incision. The findings at operation were similar to those in Case 1. The patella was excised and the defect in the patellar tendon repaired with interrupted sutures of cotton.

After six weeks this patient failed to return to the clinic. Efforts to locate her for examination were in vain.

CASE 4.—R. S., a white male, aged 20 years, was seen in Charity Hospital in New Orleans, July 14, 1940, with a slipped femoral epiphysis on the right side, which was several months old. July 20, 1940, an osteotomy through the neck of the femur was done and a Smith-Petersen nail inserted to maintain fixation. Shortly after the beginning of active exercises an effusion appeared in the right knee joint. No history of injury was elicited. The effusion was not present when the patient was first seen nor on any subsequent admission. Because the effusion was considered to be transitory and related to the physical therapy, the patient was allowed to return home wearing an ACE bandage support.



Fig. 1.—R. S., Case 4, shows fibrillated and degenerated cartilage with changes in, and infiltration of, subchondral bone; nontraumatic in origin. Compare with Fig. 2.

He was readmitted to the hospital, March 17, 1941, at which time the effusion in the right knee was still evident, but the patient had no complaints. Aspiration of the fluid in the right knee showed a clear yellowish material, with normal cell count and no growth on culture. Following aspiration a definite grating sensation was noted with motion of the patella over the femoral condyle, but this was only slightly painful. Roentgenograms of both knees showed nothing in the patellar region aside from the effusion.

A preoperative diagnosis of osteochondritis of the patella was made, and on March 27, 1941, the knee joint was opened through a median parapatellar incision. The operative findings were identical to those of Case 1. The patella was excised, and the defect in the patellar tendon repaired with interrupted sutures of black silk.

Microscopic examination of the excised patella revealed the following (Fig. 1). Section through the articular cartilage showed considerable fibrillary degeneration of the superficial portions. There was also an irregular overgrowth of degenerated fibrocartilage. In one area the osteochondral junction was disrupted and the connective tissue invaded rather deeply into the underlying bone with resorption of trabeculae. There was an irregular deposition of new bone. Portions of the osteochondral junction were fairly regular in appearance. The periosteal surface of the bone also showed fibrous thickening. There was considerable splitting of the overgrown peripherally located fibrocartilage. Sections through the synovial tissue revealed swelling of the synovial mesothelium and perivascular mononuclear and plasma cell infiltration of the capillaries and the underlying connective tissue.

Nov. 6, 1941, the patient was working in a lumber mill as a laborer without disability referable to the knee joint and without evidence of recurrence of the swelling or effusion.

CASE 5.—L. S., a Negro woman, aged 44 years, was admitted to Charity Hospital in New Orleans, March 20, 1942, because of pain and swelling in the right knee. A direct blow over the right knee sustained in July, 1941, resulted in swelling and pain in the knee joint.

On examination some thickening of the synovium was noted and there seemed to be an increase in the amount of joint fluid. The patella was freely movable with some pain in the region just lateral to the patellar margin on its medial and lateral borders. A palpable grating sensation was present upon motion of the patella over the femoral condyles. There was free motion in the right knee from 180 degrees in extension to 40 degrees in flexion. No measurable atrophy was found in the thigh or calf.

A preoperative diagnosis of osteochondritis of the patella was made, and on March 25, 1942, the knee joint was opened through a median parapatellar incision allowing the escape of a moderate amount of clear yellowish fluid. Operative findings were characteristic of traumatic osteochondritis. The patella was excised and the defect in the tendon repaired with interrupted sutures of cotton.

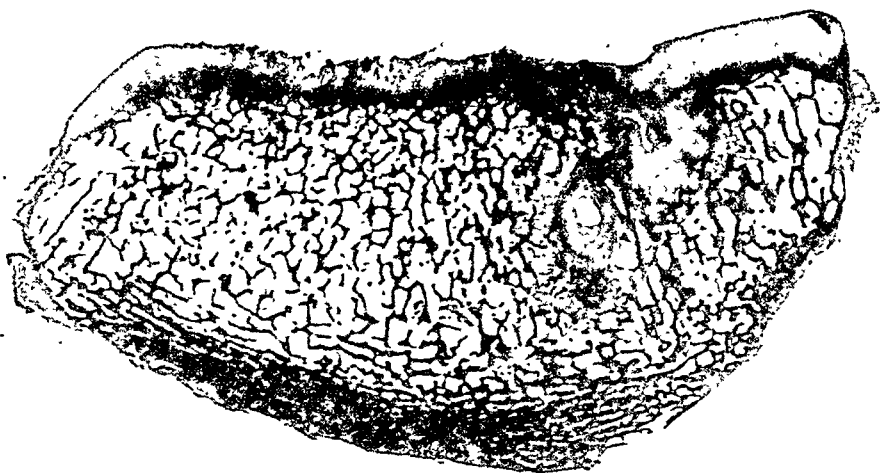


Fig. 2.—H. K., Case 6, shows extensive degeneration of articular cartilage with destruction of subchondral bone; definitely related to trauma. Microscopic picture identical with Fig. 1.

CASE 6.—H. K., a white female, aged 17 years, was complaining of pain in the right knee when she was admitted to the Hospital for Ruptured and Crippled in New York, Nov. 7, 1939.

About two and one-half years before admission, the patient struck her right knee forcibly against the cement surface of the walk when hit by an automobile. The knee continued to be painful and disabling for eighteen months. Conservative treatment was not beneficial.

Physical examination showed a low-grade effusion, some slight thickening of the synovium, and pain with extreme flexion or extension of the knee joint. The right thigh measured $2\frac{1}{2}$ inches less than the left. Crepitation and pain were produced with passive motion of the patella over the femoral condyle. The roentgenograms showed slight effusion into the joint and generalized atrophy, but no distinctive changes in the patella or adjacent femoral condyle.

Nov. 11, 1939, the right knee joint was opened through a median parapatellar incision. Pathologic changes observed at operation were identical to those in the other cases. The patella was excised.

Microscopic examination of the excised patella (Fig. 2) revealed considerable degeneration of the articular cartilage. The cells in many places showed no tendency to absorb stain at all. In the periphery the cartilage appeared well vascularized and much more cellular. Areas of necrosis in the underlying bone with evidence of attempted repair were noted.

In February, 1941, the patient stated that her right knee was comfortable. There was a normal range of motion. Some atrophy of the thigh musculature persisted, but the symptoms experienced before operation had completely disappeared.

DISCUSSION OF CASES

In all cases except one a direct injury to the patellar region was sustained which forced this bone against the anterosuperior surface of the medial femoral condyle. This resulted in immediate temporary disability, caused by local swelling and pain upon flexion or extension of the knee joint.

The acute symptoms referable to the knee joint subsided for several weeks or months. With the passage of time there appeared a low-grade chronic effusion, which fluctuated in degree with the extent and character of exercise indulged in by the patient. Definite vague symptoms of discomfort persisted within the knee joint and vague pain was felt on its anterior aspect. This sometimes was made worse by exerting strain upon the flexed knee through the quadriceps apparatus, as when kneeling or squatting. All patients complained of occasional symptoms of "locking," or "catching," which may simulate the condition commonly referred to as an internal derangement of the knee joint. The condition is a chronic one as evidenced by the fact that the average duration of symptoms in the present series (excluding the case with a history of twelve years) was 13.2 months.

The physical findings in this group of cases were typical. There was definite effusion within the knee joint; in some cases it was minimal and in others, grossly apparent. Thickening of the synovium was usually palpable. Mild pain referred to the anterior compartment of the patella was felt when the knee was acutely flexed or extended. Atrophy of the thigh varied with the severity of the symptoms produced by the lesion.

Crepitation, or "grating sensation," could be elicited upon passive motion of the patella over the articular surface of the femoral condyles. Pressure over the patella or passive motion of the patella caused pain. Occasionally, this could not be clearly demonstrated until the excessive joint fluid was removed by aspiration. Synovitis and obliteration of the suprapatellar pouch shadow by an intra-articular collection of fluid were seen in the roentgenograms but were so minimal as to be almost insignificant in most cases. Fig. 3 shows two views of the patella taken after excision. The only changes which can be seen are in the patella. These would not be visible in the routine films made preoperatively. Suggestive atrophy of the patella and femoral condyles can be seen in the film, but this is not of much diagnostic value.



Fig. 3.—Anteroposterior and lateral views of an excised patella, showing no significant changes visible in cancellous bone. The microscopic sections of this patella are shown in Fig. 1.

The following gross pathologic changes were noted at operation: (1) softening, irregularity in contour, and fissure formation in the articular cartilage of the patella; (2) yellowish discoloration of the articular cartilage in the areas of involvement; (3) similar changes in the articular cartilage of the femoral condyle on its anteromedial aspect; (4) thickening, hyperemia, and villous degeneration of the synovium, usually confined to the suprapatellar pouch region and the anterior compartment of the knee joint; (5) increase in amount of joint fluid, usually clear yellow in color with normal cell count, or slight increase in polymorphonuclear cells; (6) pannus formation at the edges of the articular cartilage of the patella and femoral condyles.

COMMENT

The changes which occur in articular cartilage as a result of direct trauma have been recognized for many years. First described by Budinger^{5, 6} in 1906, it was later clarified by König⁷ and Laewen.⁸ Attention has always been directed toward the cartilaginous changes, and

the syndrome produced has been referred to as traumatic cartilage fissuring (Budinger, 1906), chondromalacia (Konig, 1928), and chondritis (Darrach, 1935). Kulowski,⁹ Slowick,¹⁰ Herzmark,¹¹ Darrach,³ and Chaklin⁴ have all referred to the syndrome in the American literature. They ascribed the etiology to trauma and particularly emphasized the changes which were found in the articular cartilage. In my opinion the true pathologic change is to be found in the underlying cancellous bone, and the change in the articular cartilage is an entirely secondary one.

The one point of interest in the present series which cannot be properly interpreted is that absolutely no history of injury was elicited in Case 4. The patient was convalescing from an osteotomy for slipping of the upper femoral epiphysis. While the patient was still in plaster, an osteochondritic focus developed in the patella of the same extremity. The histologic picture of the excised patella in this case was almost identical to that of the other cases reported. Trauma must certainly be considered as the prime cause of this particular type of osteochondritis dissecans although we cannot conclude that it is the sole cause.

In almost every case that I have studied, or that has been reported by others, uniformly definite inflammatory changes developed in the synovium of the knee joint. In this series the synovitis was localized to the anterior compartment of the knee joint and associated with hypertrophy and thickening of the infrapatellar fat pad. Pannus formation was observed over the involved femoral condyles and the edge of the articular surface of the patella. In every instance there was evidence of the persistence of chronic synovitis, and progression of the extent of involvement of the synovium with the passage of time. If these changes exist for a long time, osteo-arthritic changes will develop. This fact is clearly brought out by a review of the available literature.^{5-10, 12} Laewen⁸ in 1925 reported thirteen cases and considered the removal of the injured cartilage as an early operation for arthritis deformans. Key¹² in 1924 emphasized that contusion of cartilage could lead to chronic progressive arthritic change. Bozan¹ attempted to explain this phenomenon in his statement, "Due to the accepted fact that these foci are aseptic, all too complete innocuity is attributed to them. Necrotic tissue, even if aseptic, elicits reaction from its surroundings. The reaction is not violent and consists mainly of edema. The edema pervades the surrounding soft tissues, increases the amount of joint fluid, and leads to spasm, stiffness, and pain." The process may be much more complicated than this. In the present group of cases, where changes were noted in the articular cartilage of the femoral condyle, this area was not disturbed. Only the patella was removed. In four instances, therefore, degenerated fibrillar cartilage was allowed to remain within the joint and if areas of aseptic necrosis in the cancellous bone of the femur existed, these were also allowed to remain. However, every one of the six patients treated by excision of the patella, with the

synovium and degenerated femoral cartilage left undisturbed, made complete recoveries, with disappearance of the synovitis and effusion in every instance. Some other factor may well be the cause of the late development of arthritic change. Removal of the involved cartilage alone has caused subsidence of the synovitis and secondary joint changes. Patellaplasty has given good results, although apparently not quite as good as patellectomy. In earlier cases with minimal changes perhaps simple resection of the involved cartilage will suffice; however, in the more severe grades with complete erosion of the cartilage it is believed that patellectomy is preferable. The fact is recognized that recently arthritic changes have been shown to develop following patellectomy in the rabbit.¹³ It is known that arthritic changes will develop if the patella is allowed to remain in situ under the present disease process in man. I am not completely convinced that removal of the patella in the human being will lead to arthritic changes in later life. Although there is no definite proof at this time, it is felt that the more severe and permanent changes resulting from an osteo-arthritis have been obviated in this group by removal of the patella. The lesion, as described, is rare by admission, but perhaps not so rare as it might seem at first glance. If the undersurface of the patella were routinely inspected in every exploratory operation for internal derangement of the knee joint, probably more cases would be encountered.

CONCLUSIONS

1. Diffuse osteochondritis of the patella can result from trauma.
2. The lesion causes a minimal amount of disability, but a real one.
3. The history is fairly typical, the symptoms chronic.
4. The physical findings are negligible.
5. If untreated for a period of years, the lesion would probably lead to irreparable damage caused by superimposed osteo-arthritic changes.
6. If symptoms persist, patellectomy will result in complete disappearance of the synovial inflammatory changes, and absolute alleviation of symptoms. By inference, it should prevent the development of osteo-arthritis in later life.

The author wishes to express sincere thanks to Dr. Phillip D. Wilson and Dr. Dominic De Santo of the Hospital for Ruptured and Crippled in New York City for arousing an interest in this subject and furnishing Case 6 of this series for study; to Dr. Guy A. Caldwell and Dr. R. H. Allredge of the Tulane University School of Medicine for allowing him to continue this study to its present point.

REFERENCES

1. Bozan, E. J.: Compression of Cancellous Bone; Principal Manifestations in Head and Neck of Femur; Treatment by Connecting Drill Channels, *Am. J. Surg.* 53: 537, 1941.
2. Darrach, W.: Chondritis of the Knee, *Ann. Surg.* 110: 948, 1939.
3. Darrach, W.: Internal Derangements of the Knee, *Ann. Surg.* 102: 129, 1935.
4. Chaklin, V. D.: Injuries to the Cartilages of the Patella and the Femoral Condyle, *J. Bone & Joint Surg.* 21: 133, 1939.
5. Budinger, K.: Loosening of Joint Tissues and Resulting Phenomena, *Deutsche Ztschr. f. Chir.* 84: 311, 1906.

6. Budinger, K.: Traumatic Cartilage Fissuring in the Knee Joint, Deutsche Ztschr. f. Chir. 92: 510, 1908.
7. König, G.: Arthritis Deformans and Surgery, München. Med. Wehnschr. 75: 32, 1928.
8. Laewen, A.: Knorpelresektion bei fissuraler Knorpeldegeneration der Patella —eine Frühoperation der Arthritis Deformans, Beitr. z. klin. Chir. 134: 265, 1925.
9. Kulowski, J.: Chondromalacia of the Patella, J. A. M. A. 100: 1837, 1933.
10. Slowick, F. A.: Traumatic Chondromalacia of the Patella; Report of Two Cases, New England J. Med. 213: 160, 1935.
11. Herzmark, M. H.: Traumatic Degenerative Fibrillation of the Patella, J. Bone & Joint Surg. 19: 1089, 1937.
12. Key, J. A.: Contusion of Cartilage as an Etiological Factor in Chronic Arthritis, Surg., Gynec. & Obst. 58: 166, 1934.
13. Bruce, J., and Walmsley, R.: Excision of the Patella, J. Bone & Joint Surg. 24: 311, 1942.



TREATMENT OF TENDONS IN FINGER AMPUTATIONS AND DESCRIPTION OF A NEW INSTRUMENT

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DISPOSITION of severed tendons in finger amputations is a matter on which there is some diversity of opinion. The teachings of most published works on operative surgery recommend some form of suturing the tendon ends to the tendon sheath or to the bone in order to preserve the greatest function of the fingers.

Kirk¹ advocates the following procedure for a metacarpophalangeal disarticulation: "The finger is hyperextended and flexor tendons cut and allowed to retract in their sheaths. The finger is flexed, the extensor tendon cut, and with a small, sharp-bladed knife the joint is opened, the capsular ligament cut around and the finger removed."

This hyperextension of the finger, allowing the flexor tendons to retreat in their sheaths, gives a very useful hand. Attempts to secure the tendons to the sheaths at the point of division of the tendon, or even worse, suturing the flexor to the extensor over the end of the metacarpal stump, produces an unusual type of disability, with loss of the grip and inability to flex the fingers into a tight fist (Figs. 1, 2, and 3).

The mechanism of this disability is interesting and is related to the common origin of the flexors, particularly the profundus group, so that tension on any one tendon restricts, partially, the excursion of the others. This is best demonstrated in the normal hand by holding one's middle finger straight in line with the metacarpals, then trying to close the other fingers into a tight fist. The fingers cannot be entirely closed, and there is pain in the forearm and hand as this is attempted.

In amputations through the proximal phalanx, it is common practice to suture tendons to tendon sheath. This is satisfactory if the finger is hyperextended before the tendon division, but it is unnecessary for finger function and occasionally results in disability if the tendons become adherent while under slight tension. The difference in excursion of the sublimis and profundus tendons has been accurately measured by Bunnell² and consideration of this difference makes illogical the suturing together of both tendons in the sheath.

It is better practice to allow the tendons to retract within the sheath, or if they are densely adherent, as from an old injury, both profundus and sublimis should be stripped out to allow free motion (Figs. 1, 2, 3, and 4). Control of the proximal phalanx is exercised through the

The opinions or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

Received for publication, July 10, 1944.

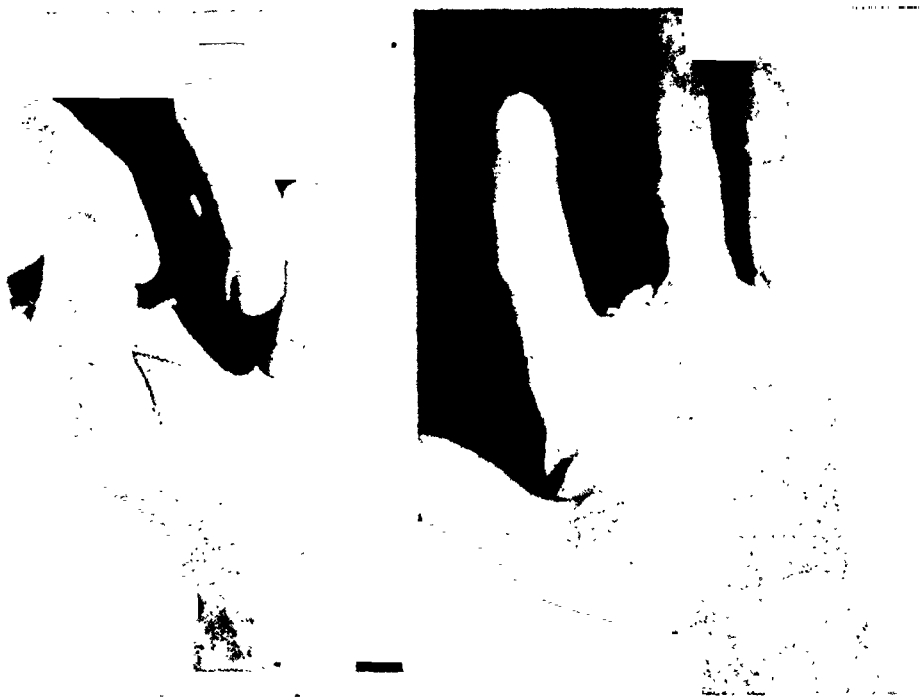


Fig. 1.—Disability produced by suturing flexor sublimis and flexor profundus tendons of the middle finger to the extensor tendon over the distal head of the metacarpal in a metacarpophalangeal disarticulation. Patient cannot close fingers to make a fist and cannot extend them completely.



Fig. 2.—Same patient as shown in Fig. 1 after total excision of flexor sublimis and flexor profundus tendons. Note the small transverse scar at the wrist through which proximal ends of tendons were severed. Full function is present.

digital extensor complex, which has been described in minute detail elsewhere.⁹ Essentially, this extensor complex, composed of lumbricals and interossei, acts as a flexor of the proximal phalanx when it passes volarward beyond the midline of the flexion axis of the metacarpophalangeal joints. The interossei, which carry the greatest load in this motion, are very strong and give an excellent grip.

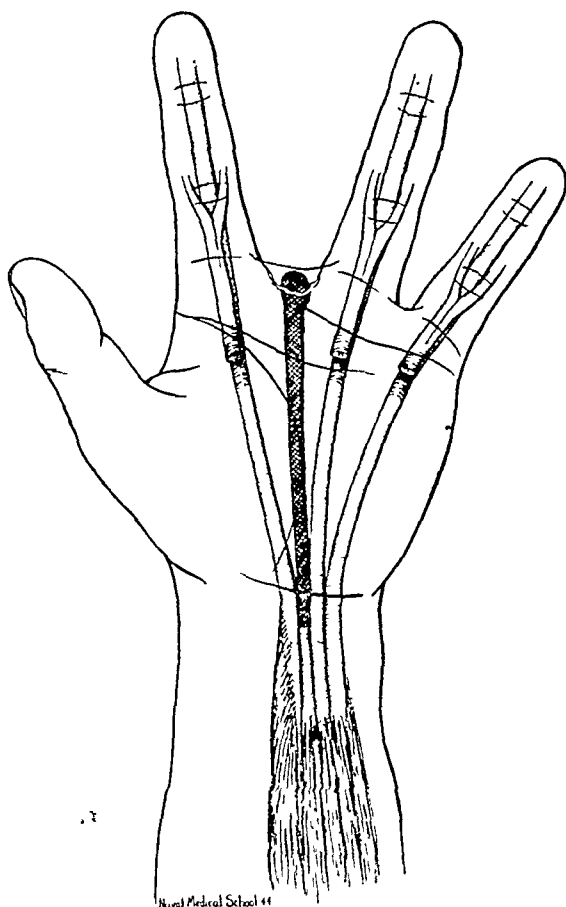


Fig. 3.—Schematic drawing, showing position of tendons excised (black, cross-hatched area). The common origin of the flexors illustrates the reason for the disability shown in Fig. 1.

Disarticulations at the distal interphalangeal joints or amputations in the middle phalanx are best treated by dividing the flexor profundus tendon and allowing it to retract (Fig. 5). This practice has been amply supported by Stevenson⁸ and others and gives a better grip than does suturing the tendon to the sheath.

Amputations in the terminal phalanx rarely involve tendon division, for if they are distal to the tendon insertion in the buttonlike base of the terminal phalanx, the tendinous attachment is left intact. Reattachment of the severed flexor profundus insertion should be carried out if avulsion has occurred.

Extensor tendons do not retract appreciably and if left alone will become adherent to the underlying bone, and function quite well. Here, of course, there is no problem of any tendon sheath. In the thumb, tendons should be preserved and sutured to the bone with tension as nearly normal as possible.



Fig. 4—Specimen obtained at surgery. The lumbrical muscles are still attached to the flexor profundus tendon

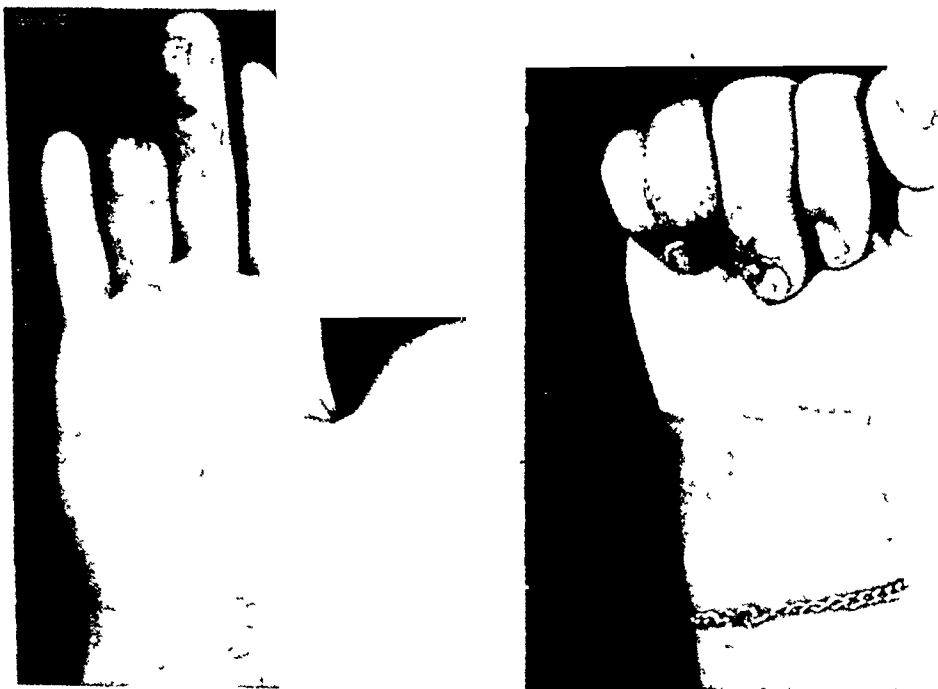


Fig. 5—Recently healed traumatic amputation of ring finger in which flexor profundus tendon was cut and allowed to retract. There is excellent function of the stump and of the other fingers

AMPUTATIONS IN CONTAMINATED OR INFECTED CASES

Although the foregoing discussion has applied to clean cases, it is frequently necessary to amputate a digit in the presence of contamination from immediate trauma. In exceptionally clean cases, the tendons can be allowed to retract, but where contamination is excessive in very dirty wounds, or where blood supply has been impaired or tendons fragmented, the possibility of spreading infection more proximally in the hand must be borne in mind. In such cases and in frankly infected cases, the tendon or tendons should be sutured to *one side* of the tendon sheath, securing it against retraction, and leaving the remainder of the sheath *open* for drainage.

Function following such procedures may or may not be good, depending on the location of the tendon division and the tension on the tendon stump. Whatever the resulting function, it is secondary in importance to maintenance of integrity of the protective barriers against bacterial invasion, and function can be dealt with later when the wounds are well healed. Fragmented tendons are excised or trimmed back to viable tendon, all foreign particles are removed, and copious saline irrigations are used to wash away unseen debris. Sterile normal saline dressings are applied at the operating table and continued while the patient is in the ward in those cases where primary closure is not elected.

LATER RECONSTRUCTION SURGERY

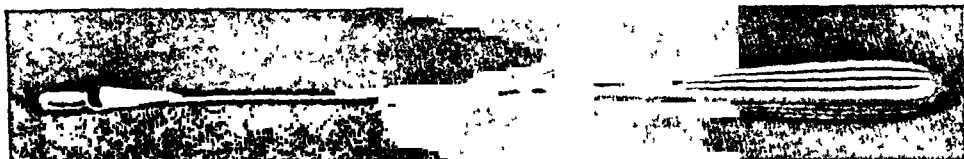
When the destructive phases of infection have passed, masses of dense scar restrict movement and bind tendons, sheaths, and surrounding tissues into a functionless inelastic cicatrix. In an intact finger, tendons may be freed from scar and attempts made to restore the delicate gliding mechanism, usually by a free tendon graft, as advocated by Mayer,⁷ Bunnell¹ and Mason,⁵ and now almost universally employed. Mayer⁷ stated that "In old cases, it is wise to excise the scarred remnants of tendon entirely and replace with a free graft of tendon sheath."

In an amputated finger, however, it is rarely, if ever, advisable to put in a new tendon, or repair the old, and excision of the scarred flexors in their entirety gives a better functioning stump. With amputation distal to the insertion of the flexor sublimis digitorum, an attempt should be made to preserve the sublimis tendon and strip out the profundus. A free graft of long-fibered sliding fat from the lateral thigh or triceps tendon regions, as advocated by Bunnell, is most useful in this connection, implanted about the rough tendon to restore its gliding mechanism. A pedunculated flap of fat, as suggested by Kanavel,³ would not be a practical procedure in an amputated digit.

A NEW TENDON STRIPPER

The removal of a densely adherent tendon from its scarred bed would require extensive incisions in the hand if one sought adequate exposure

of its entire length. Excision through small transverse incisions in the hand and wrist can be carried out nicely with smooth tendons which strip easily from normal surrounding tissues. An adherent tendon must be freed and a ringlike stripper has been designed (Fig. 6) with a long thin handle to dissect such adhesions and free the tendon in much the same manner as Masson's fascia stripper² is used to remove long strips of fascia lata through a small incision in the thigh. The tendon can then be severed through a second small transverse incision in the wrist (Fig. 2), obviating the need for the double-tubed sleeve-cutting device of Masson.



A.



B.

Fig. 6.—A, Author's instrument for stripping adherent tendons in the palm when one end of the tendon is severed, as in a finger amputation B, Close-up of cutting tip of stripper.

Bunnell¹ developed tendon strippers many years ago and they are in general use today. His development of the stripper was for a slightly different purpose at that time. He states that: "When a tendon that is imbedded in adhesions is freed, the surface of the tendon is usually very ragged and hacked. To avoid this, it is well to use the tendon stripper to be described further." Later he describes their construction originally from a set of nested cork borers.

The slotted stripping sleeve of the Bunnell stripper allows its application to an intact tendon, both ends of which are attached. The stripper

described herein for excision of tendons in an amputation stump is fitted over the severed end of tendon and is guided through the palm on the tendon. In this manner, chance slipping of the cutting edge during sometimes vigorous division of adhesions cannot occur and injury to important nerves and vessels in the palm is thus prevented.

SUMMARY

Flexor tendons need not be sutured to bone or tendon sheath in clean cases and must not be overlapped and sutured over the end of the bone to the extensor tendons. Disability, with weakness of the grip, results. In contaminated or infected cases, they should be anchored at the point of amputation and the tendon sheath left open to avoid spread of infection to the hand. Such tendons may become adherent and produce disability. They should be excised to free the finger, relying on the intrinsic muscles of the hand for motion of the stump. A tendon stripper, suitable for freeing such tendons in the hand, is described.

REFERENCES

1. Bunnell, Sterling: Repair of Tendons in the Fingers and Description of Two New Instruments, *Surg., Gynec. & Obst.* 26: 103, 1918.
2. Bunnell, Sterling: Primary Repair of Severed Tendons—the Use of Stainless Steel Wire, *Am. J. Surg.* 47: 502, 1940.
3. Kanavel, Allen B.: *Infections of the Hand*, Philadelphia, 1925, Lea & Febiger.
4. Kirk, N. T.: Amputations, and Dean Lewis, *Practice of Surgery*, W. F. Prior Company, Inc. III-10:24.
5. Mason, M. L.: Primary and Secondary Tendon Suture; Discussion of Significance of Technique in Tendon Surgery, *Surg., Gynec. & Obst.* 70: 392, 1940.
6. Masson, J. C.: New Instrument for Securing Fascia Lata for Repair of Hernia, *Proc. Staff Meet., Mayo Clin.* 8: 529, 1933.
7. Mayer, Leo: The Physiological Method of Tendon Transplantation, *Surg., Gynec. & Obst.* 22: 182, 1916.
8. Stevenson, Thos. W.: Personal communication.
9. Webster, Geo. V.: Simple Fractures of Metacarpal Diaphysis, *U. S. Nav. M. Bull.* 42: 623-640, 1944.

MODIFIED CALIBRATED SKIN-GRAFTING KNIFE

FURTHER OBSERVATIONS

MAJOR KERWIN M. MARCKS, MEDICAL CORPS, U. S. ARMY

I AM presenting this paper as a supplement to a recent article^{*} describing a modified calibrated skin-grafting knife. Reports of the use of this knife have been very encouraging. Personal communications from Kilner in London, Doud in the European theater of operations, and surgeons in this country have described gratifying results. In my previous paper I neglected to advise as to the method of using the knife, and shall attempt to rectify this by giving a few simple instructions.

The size of the graft to be cut will depend on the surface area of the donor site, the amount of skin required, and the ability and patience of the operator. For skin traction I prefer the Blair-Brown suction cups, with the assistant holding a board for countertraction. A board or pan can be used, however, in the place of the suction cups to keep the skin as level as possible, and also on slight tension. Petrolatum jelly is then applied to a previously prepared donor area. The attachment is regulated according to: (1) the thickness of skin desired; (2) the area from which the graft is to be taken; (3) the age of the patient; and (4) the condition of the skin. The knife is placed flat and firm on the skin, but not with too much pressure, and a sawing motion is begun. The rod should remain stationary during the cutting of the graft, except for its rolling motion, with the graft presenting between the rod and the blade and rolled up over the blade of the knife, as illustrated in Figs. 1 to 7.

Tilting the knife away from its parallel position might increase or decrease the thickness of the graft and cause the rod to move with the knife. This defeats the purpose of the thickness-determining factor and should be avoided. Should the graft be too thick or too thin, correction is made by adjusting the thickness-regulating screws. The adjustment can be readily accomplished without removing the knife from the donor site, simply by turning the screws clockwise to increase the thickness of the graft and counterclockwise to decrease the thickness of the graft. When the cutting is completed, the graft is placed between layers of warm saline gauze, and the donor area is dressed according to the usual custom of the operator.

The care of the knife after cutting the graft is important. A sharp knife is essential, and it should demand the respect of the operator at all times. I present the knife to the nurse after using. She removes

Received for publication, July 8, 1944

*Marcks, K. M.: Modified Calibrated Skin-Grafting Knife, *Mil. Surgeon* 92: 653, 1943.

the rod, washes it with warm water, and then with ether. She then places a small amount of petrolatum jelly on the blade, replaces the rod, and wraps the assembly in a towel. When the knife is to be used, I remove the rod and the attachment, wash with ether, and strop the blade with emery powder on a wet towel according to the directions of Blair and Brown for the care of the Blair-Brown knife. The knife is then wiped with the wet towel, dried, and the attachment replaced. It is placed in 70 per cent alcohol until ready for use, when it is washed with sterile water and dried with sterile gauze. Kilner uses a three-way strop and gets excellent results.

A.



U.S. ARMY MEDICAL MUSEUM

B.

Fig. 1.—A, Microphotograph of section of skin cut with the assistant turning thickness-determining screws in order to increase the thickness of the graft while the graft was being cut. Knife did not leave skin during the cutting of the graft.

B, microphotograph shows self-adjustment while cutting graft. The thinner split graft was cut, the adjustment made at the central depression area, and then the thicker split graft cut without removing knife from skin.

Both these specimens were cut for slide demonstration purposes.

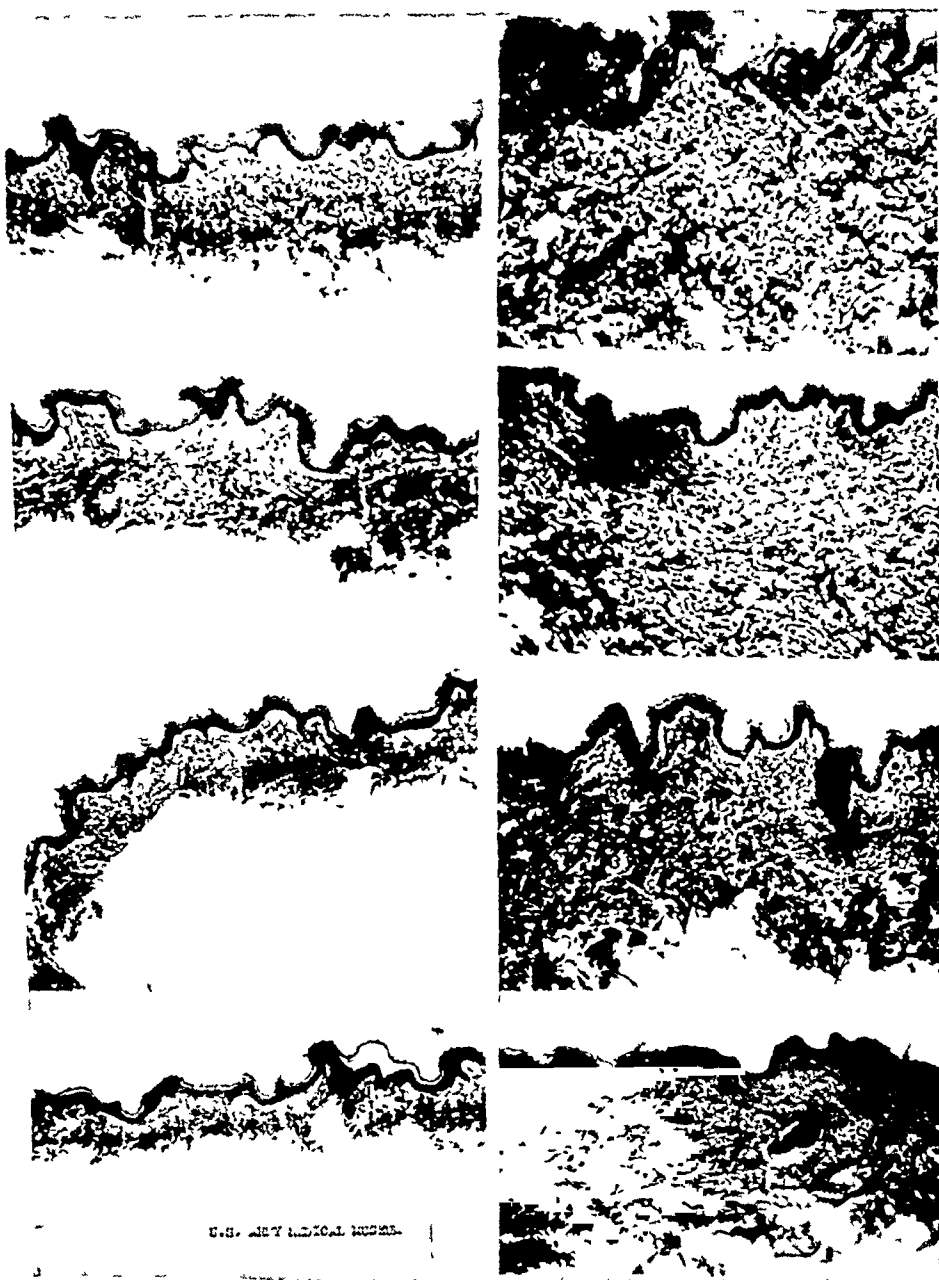


Fig. 2.—Microphotographs show various thicknesses of split grafts cut with the described modified calibrated skin-grafting knife.

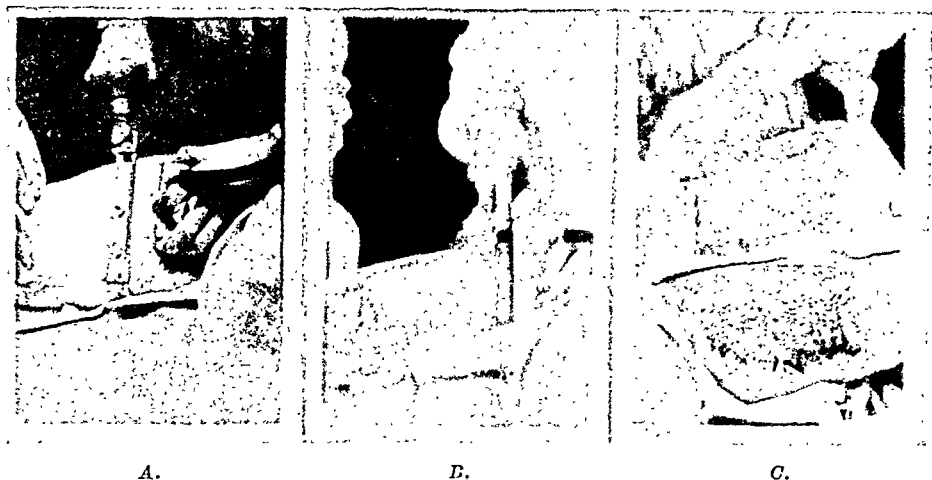


Fig. 3.—Illustration of the cutting of a split graft with the modified skin-grafting knife. The end of the procedure is seen in *B* and the donor area and graft *C*. The inside of the thigh, when available, is an ideal location for the cutting of a large graft and in my experience is more frequently used than any other donor site.

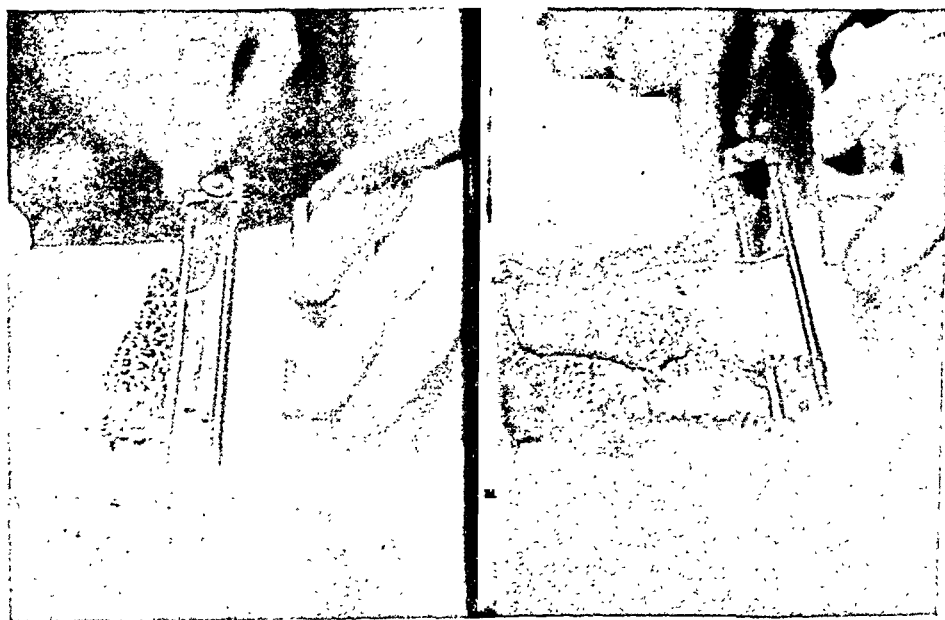


Fig. 4.—Illustration of the cutting of a thicker split graft from the thigh. Notice the amount of retraction of the graft as compared to the thinner graft in Fig. 3.

How often should the knife be honed? This is a difficult question to answer and must be left to the judgment of the surgeon. I have cut thirty-three grafts with one of my blades before I felt honing was necessary.

The cutting of a graft with this appliance should offer no difficulty if one is accustomed to the cutting of a graft with a straight blade. If one is not accustomed to cutting grafts, practice may be necessary. To determine the thickness to be cut, I simply hold the knife to the light to observe the space between the blade and the rod. However,

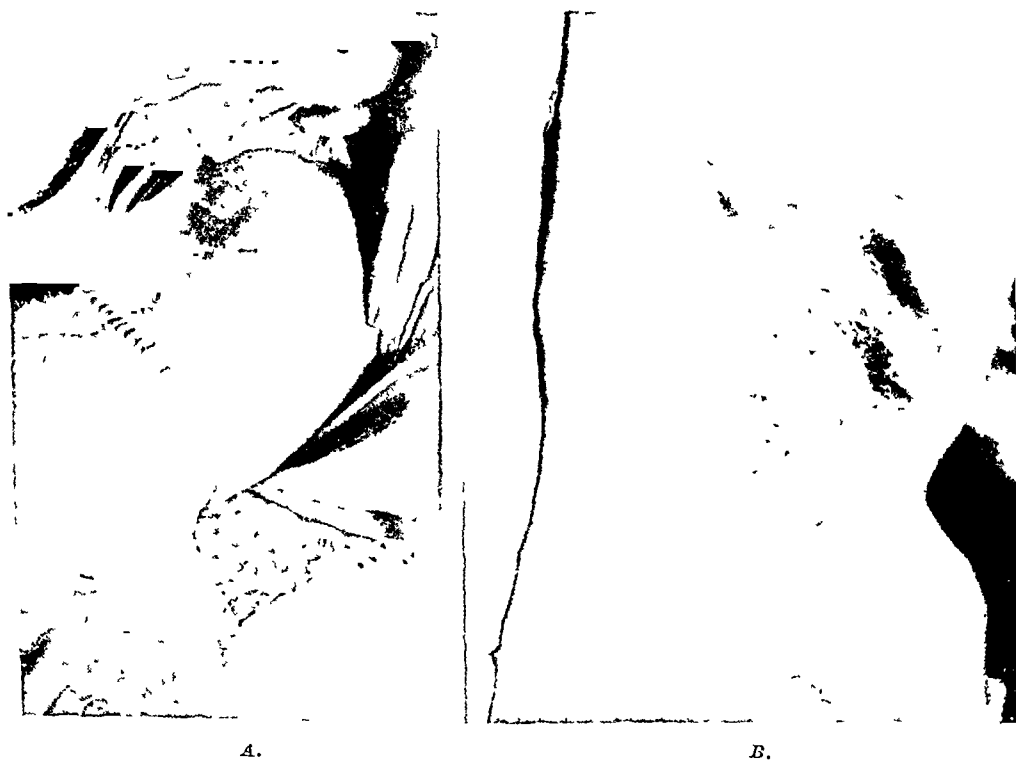


Fig. 5—Donor areas on the back. Both of these patients had burns of the legs. The anterior and lateral surfaces of one thigh were used. A small split graft was still necessary to cover the granulating area on the posterior surface of one of the legs and the back was readily available as a donor site. In B, donor areas are shown on the back. The edges show a great deal more irregularity as compared to A, but the graft was placed on granulating surface and this factor was not important. An emaciated back like this may offer considerable difficulty in cutting a graft.

there are graduations which may be used to determine the thickness. For this purpose, the screw must be turned counterclockwise until the rod touches the blade. This will be the zero index. Then the screw must be turned clockwise to the desired number of graduations past the zero index necessary for a particular thickness of graft desired.

There is one difficulty that may arise in cutting the graft. A satisfactory graft may be cut with one end of the knife, but the other end may appear thicker in spite of equal calibration. In this case it might be

well to check the width of the blade because, if the blade is so wide that its edge lies opposite the center of the rod or extends beyond the center of the rod at either end, the disturbance mentioned will result. This can be corrected by sending the knife to the manufacturer for honing, so that the width of the blade is made equal throughout and so that, when the screws are turned down, the edge of the blade will strike the rod everywhere just proximal to the center of the rod.

A.



B.

Fig 6.—Donor areas on the side of the upper arms. Notice the keloid formation on the donor area of the Negro patient (A). This is another convenient and practical donor site. Quite a wide graft can be cut from this region by having the operator place his foot on a stool, grasping the patient's arm and placing it across his thigh, thus resting the upper arm and increasing the surface area.

Finally, I wish to stress the importance of considering the age of the patient, location of the donor area, and condition of the skin from which the graft is to be cut, since these factors are variable. If good sound surgical and anatomical judgment is always employed, this instrument will serve a good purpose.

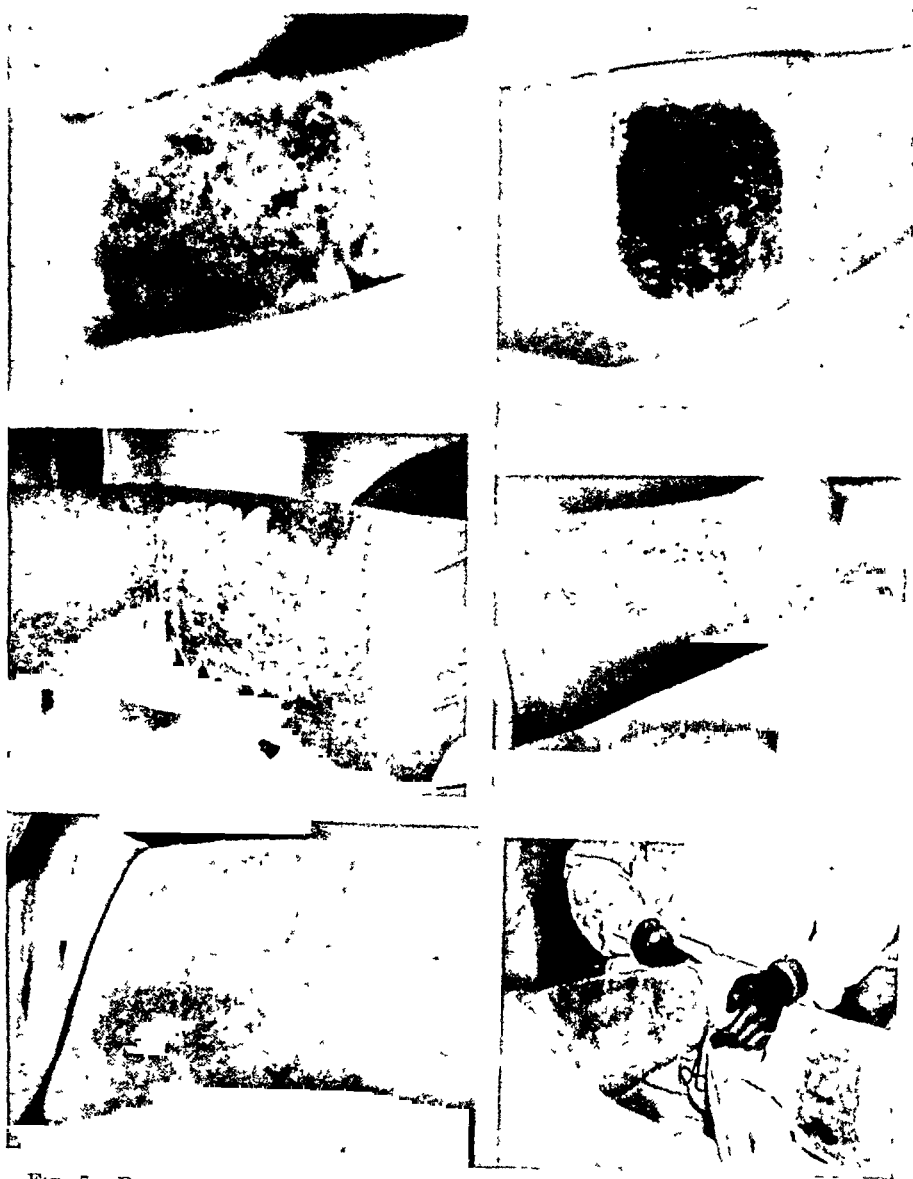


Fig 7.—Donor areas on the inside thigh regions. As mentioned previously, the thigh is an ideal donor site and extremely valuable when a wide and long graft is necessary to cover an extensive denuded area. The edges of the donor areas are not always this regular when this knife is used but after practice, trial and error, and with a moderate amount of patience, a nicely shaped graft can be removed with the resultant donor areas as shown here.

SUMMARY

I have presented a supplement to a previous paper illustrating the use of the attachment to the Blair-Brown skin-grafting knife for the cutting of split grafts.

ANESTHESIA FOR THE BURNED PATIENT

CAPTAIN E. M. PAPPER, MEDICAL CORPS, ARMY OF THE UNITED STATES

BECAUSE of the large number of burns among the casualties of modern warfare, considerable interest has been manifested in the various aspects of the treatment of the burned patient. Extensive studies, experimental and clinical, have been presented on the problems of pathologic physiology and the clinical management of burns, with particular emphasis upon the control of plasma loss and shock with plasma replacement therapy, and also upon the factors concerned with the local treatment of the burned areas. Despite the interest in the problem of burns and the mass of material available for study, comparatively little attention has been paid to the importance of the anesthetic management of the burned patient who requires operative procedures either early or late in the course of the injury.

Generally speaking, the consensus has been that the surgical treatment of acute burns should be performed without anesthesia where possible.¹ However, there are many instances in which the employment of an anesthetic is necessary to the successful completion of a surgical procedure in the burned patient. In this connection pentothal sodium has been recommended by several authors as the anesthetic of choice.²⁻⁵ Other writers have administered nitrous oxide⁶ and ether.⁷ In so far as can be determined from a study of the available literature, the employment of infiltration, nerve block, or spinal anesthetic procedures has not been advocated in the therapy of the acutely burned patient. In the reconstructive aspects of therapy for the burned patient no definite stand has been taken with regard to the choice of anesthesia by workers interested in this subject, except for the group at the Massachusetts General Hospital who cared for the patients of the Cocoanut Grove disaster.⁸ In this series, twenty-one operations of a plastic nature were performed with ether as the agent of choice in thirteen, and a variety of agents and techniques for the remainder. The statement is made that no complications due to anesthesia were noted in any of the cases described.

Because of the relative paucity of information available as to the factors concerned in the proper anesthetic management of the burned patient, both in the acute and in the late or chronic stage of the injury, a summary of experience available at a large Army General Hospital appears to be in order.

CLINICAL DATA

Since the clinical material was observed at a Zone of Interior Army General Hospital, little opportunity was afforded to treat acute thermal

burns immediately after injury. Of the patients admitted with acute burns, only six required emergency surgical intervention in the form of débridement. Two of these six were satisfactorily managed with morphine analgesia; three required pentothal sodium in very small amounts; and one, a child, was given ether by open drop technique. Since burned patients are rarely admitted to this hospital immediately after injury and are usually seen several weeks after sustaining the burn, no conclusions can be drawn based upon personal experience, but I concur in the attitude that, where possible, simple morphine analgesia is the method of choice for pain relief in the surgical management of acute burns. It should be emphasized, also, that the administration of pentothal sodium alone in the very severely burned patient is fraught with considerable danger in view of the extensive military experience in a theater of military operations,⁹ where it was shown that this drug is tolerated poorly by these patients and should be avoided.

More information was obtained in the anesthetic conduct of patients in the period suitable for skin grafting and plastic surgical procedures. Twenty-seven such patients, upon whom forty-nine skin grafting procedures were performed, were admitted in a period of twenty months. The extent of the burn varied from 5 to 50 per cent of the body surface, as estimated by the section of plastic surgery in accordance with Berkow's formula.¹⁰ In most instances, split-skin grafts were applied to the burned surfaces. The anesthetic methods consisted of spinal anesthesia for three operations in which only the lower extremities were involved in donor and recipient areas, nerve block for one procedure, ether employing carbon dioxide absorption technique in fifteen operations, and sodium pentothal (2½ per cent) supplemented with 50 per cent nitrous oxide and oxygen in thirty instances.

Premedication consisted of morphine and atropine subcutaneously approximately one hour preoperatively in cases in which pentothal was used, morphine and scopolamine in suitable doses one to one and one-half hours preoperatively for those in which ether was used, and the addition of a barbiturate to the latter for the spinal and regional anesthetics. The dosage of these drugs was somewhat less than would have ordinarily been administered because of the varying degrees of debility encountered in the patients. Earlier in the series scopolamine was given with morphine prior to the pentothal anesthesia, but the occurrence of two cases of marked laryngospasm resulting in asphyxia suggested a change to atropine as a more effective means of blocking the parasympathetic nerve endings in the larynx.⁹ The more adequate prevention of laryngospasm by atropine prior to pentothal anesthesia was supported by experience in anesthesia for patients other than those in the burn group.

During the surgical procedures, a slow drip of normal saline solution was maintained to keep the intravenous needle patent at all times and

to provide a ready portal for the administration of plasma or whole blood. In general, plasma was substituted for the saline drip if operating time extended beyond one and one-half hours. If anemia was present preoperatively or if extensive bleeding occurred during operation, whole blood was administered as the fluid of choice.

In keeping with what is considered good anesthetic practice for this type of operation, the depth of anesthesia in the etherized patients was never permitted to be more profound than light second plane of surgical anesthesia. For the most part, patients were maintained in the first plane. In the patients anesthetized with the pentothal nitrous oxide sequence, the depth of anesthesia was such that at no time was respiratory activity grossly depressed. In fact, the attempt was made to maintain anesthesia only to the extent of preventing movement on the patient's part while on the operating table.

Complications attributable to anesthesia during the performance of the surgical procedures were limited in the pentothal nitrous oxide group to two cases of severe laryngospasm, requiring intratracheal intubation, described previously. This complication, it is believed, was obviated in the succeeding cases in the series by the substitution of atropine for scopolamine in the premedicant drugs administered. In the etherized patients, four of the fifteen so anesthetized in the planes described exhibited significant circulatory depression characteristic of surgical shock. With regard to the patients anesthetized with spinal or nerve block techniques, no untoward episodes were noted, but these procedures were too small in number and were of so minor a nature that the appearance of deleterious manifestations was not to be expected. It should be noted that the magnitude of surgical manipulation was similar in patients to whom ether and pentothal were administered, requiring two to five hours for the completion of operation.

In the postoperative period several observations of interest were made by way of comparison of the various anesthetics employed. There was no apparent difference in the success of viability of the graft with regard to the anesthetic employed. There was no significant change in the hematologic picture of the four patients anesthetized with spinal and regional techniques. There was a moderate depression of both red blood count and hemoglobin in the patients anesthetized with pentothal sodium, requiring an average per patient of one whole blood transfusion consisting of 500 c.c. in the immediate postoperative period. The patients anesthetized with ether exhibited a more significant anemia postoperatively, requiring on the average three blood transfusions of 500 c.c. each in a similar period of time. It should be mentioned that transfusion was given to all patients until the red blood count had reached a minimum of 3,500,000 per c.mm. with a proportionate concentration of hemoglobin. It is evident, therefore, that in patients in whom general narcosis was considered necessary for skin grafting procedures in the

treatment of burns, the pentothal sodium nitrous oxide sequence exerted a less harmful effect upon the final picture in the peripheral blood than did ether.

Some light is cast upon the present controversy concerning the concurrent use of sulfonamide drugs and barbiturate anesthesia.¹¹ All patients observed were given one or more drugs of the sulfonamide group preoperatively and immediately postoperatively. No demonstrable ill effects were noted in the patients anesthetized with pentothal sodium and no synergism between the two was seen. In fact, as pointed out, the course subsequent to operation in the patients anesthetized with pentothal was, on the whole, more benign than that of the etherized patients, despite the use of sulfonamide preparations. The present practice at this hospital is to utilize sulfonamide drugs, regardless of the type of anesthesia to be employed, prior to operation upon the burned patient.

There were no deaths in this series of burned patients subjected to skin grafting procedures.

DISCUSSION

In considering the choice of anesthesia for the burned patient, as has indicated, the acutely burned patient presents an entirely different problem from the patient who requires plastic surgery in the later stages of the injury. The cardinal principle of treatment for acute burns is, of course, the replacement of lost plasma by proper intravenous administration of plasma itself, or a suitable substitute. Surgical procedures should be confined to a bare minimum and the patient's condition as a whole is the important problem of therapy. For pain relief the administration of morphine is probably the least harmful and the most satisfactory method of analgesia. Where necessary, small doses of pentothal anesthesia¹² or ether anesthesia⁷ may be considered acceptable but not ideal. It should be re-emphasized that the administration of any type of anesthesia producing general narcosis is not without danger in the acutely burned patient. Nerve block and infiltration techniques are useful only if the body surface burned is small in area or if the regions are supplied by accessible peripheral nerves. The employment of spinal anesthesia, particularly if the areas involved are above the tenth thoracic segment, is of considerable danger in the acutely burned patient because of the attendant circulatory depression produced by this type of anesthesia in the patient whose circulation is already impaired, either actually or potentially.¹³

In the proper anesthetic management of the burned patient in the stage of plastic repair, certain surgical requirements as well as nutritional disorders commonly seen in these patients must be borne in mind. It is desirable to maintain, in so far as possible, normal contours of the various parts concerned. This requires a reasonable maintenance of muscular tone underlying the recipient skin areas. Further, it is of

great importance in this type of surgical manipulation that a free airway be maintained to prevent capillary and venous oozing, which may result from obstructed respiration and is an important factor in decreasing viability of skin grafts. Finally, these patients very commonly suffer from anemia which requires consideration in the administration of anesthesia. Nerve block and infiltration techniques are suitable when the areas concerned in the skin grafting procedures are small enough in size to be adequately anesthetized in this fashion. If the areas concerned in the operative procedures are below the umbilicus, spinal anesthesia is considered without danger to these patients. However, as is frequently the case, either donor or recipient area will be high on the abdomen or thorax. Patients with anemia or debility do not tolerate high spinal anesthesia satisfactorily, and this technique should be avoided if the operative procedures are in the locations mentioned.

If some form of general narcosis is selected, the importance of a free airway cannot be overemphasized. If the patency of the airway cannot be assured by ordinary procedures, the employment of an intratracheal mechanical airway is indicated. This aid to respiration is necessary not infrequently and is mandatory in a position such as the prone, where ease of respiration is difficult. I am of the opinion that pentothal sodium nitrous oxide anesthesia is preferable to ether anesthesia because of the absence, in this series, of circulatory complications during anesthesia with the former, as contrasted with the latter, and the more salutary postoperative period with regard to the concentration of red blood cells and hemoglobin in the peripheral blood.

Regardless of the type of anesthesia or the drug selected, repeated emphasis is made upon the necessity for the administration of plasma or whole blood as needed during and after skin grafting procedures upon the burned patient.

SUMMARY

1. In the anesthetic management of the acutely burned patient, morphine for analgesia is the drug of choice. If morphine is inadequate, pentothal sodium or ether may be used in minimal quantities.

2. Clinical experience with various types of anesthesia in the skin grafting stage of the treatment of burns is presented. The advantages and disadvantages of the commonly employed anesthetic drugs and techniques are presented.

3. Where general narcosis is indicated for plastic surgical procedures in the management of burns, the most satisfactory results have been obtained with the employment of pentothal sodium supplemented by 50 per cent nitrous oxide in oxygen.

4. Adequate intravenous replacement therapy with plasma or whole blood, as indicated, is necessary during the operative period in the management of the burned patient.

5. The concurrent use of sulfonamide drugs and pentothal sodium exerts no clinically demonstrable ill effects.

REFERENCES

1. Circular Letter No. 161: Treatment of Burns, Washington, D. C., Sept. 11, 1943, Office of the Surgeon General.
2. Gordon, R. A.: Problems of Anesthesia in Plastic Surgery, *Anesthesiology* 3: 507-513, 1942.
3. Bishop, Harold F., and Rudder, Fred F., and discussion by Fulton, J. Roy: Intravenous Anesthesia, *J. A. M. A.* 120: 807-810, 1942.
4. Ross, James A., and Hulbert, K. F.: Treatment of 100 War Wounds and Burns, *Brit. M. J.* 618-621, 1941.
5. Coley, Bradley L.: Care of the Injured in Combat Zones, *Surg., Gynec. & Obst.* 78: 66-75, 1944.
6. Harkins, Henry N.: The Local Treatment of Thermal Burns, *Ann. Surg.* 115: 1140-1151, 1942.
7. Committee on Chemotherapeutic and Other Agents and the Committee on Surgery of the Division of Medical Sciences of the National Research Council: Prevention of Infection in Wounds and Burns, *War Med.* 2: 488-496, 1942.
8. Cannon, Bradford: Management of the Coconut Grove Burns at the Massachusetts General Hospital. (a) Procedures in Rehabilitation of the Severely Burned, *Ann. Surg.* 117: 103-110, 1943.
9. The Bulletin of the U. S. Army Medical Dept. No. 76: Pentothal Sodium, Washington, D. C., 1944, Office of the Surgeon General, p. 1-3.
10. Berkow, Samuel G.: A Program for the Emergency Treatment of Extensive Burns, *U. S. Nav. M. Bull.* 41: 946-952, 1943.
11. Adriani, John: Effect of Anesthesia Upon Chemotherapy With Derivatives of Sulfonic Acid, *South. M. J.* 35: 999-1002, 1942.
12. Editorial: The Question of Intravenous Anesthesia in War Surgery, *Anesthesiology* 4: 74-77, 1943.
13. Papper, E. M., Bradley, S. L., and Rovenstine, E. A.: Circulatory Adjustments During High Spinal Anesthesia, *J. A. M. A.* 121: 27-31, 1943.

ORTHOPEDIC SURGERY FOR RECONSTRUCTION OF CONGENITAL MALFORMATIONS OF THE KIDNEY

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INTRODUCTION

SINCE the introduction of a systematic use of urographic examination, anomalies of the kidney have been very readily discovered. It has been found that more than 50 per cent of these anomalies were responsible for painful symptoms, which in many instances had been erroneously diagnosed and many patients had even been submitted to an unnecessary abdominal operation.

The object of this paper is to call attention to the possibility of the surgical orthopedic correction of certain congenital malformations of the kidney, by applying to surgical urologic conditions the same conservative principles that have been applied successfully in orthopedic reconstructions of other systems of the body. The idea is not a new one, yet it appears that the medical profession in general has not fully grasped the fact that malformations of the kidney are not infrequently responsible for obscure abdominal symptoms.¹ Members of the profession are apparently unaware that in such cases it is now frequently possible to relieve symptoms and effect a cure by the conservative orthopedic reconstruction of a congenitally anomalous kidney.²

We are living in an era in which malformations of the kidney can be diagnosed clinically before post-mortem, and in which results can be verified by the modern methods of urologic and urographic examination. The kidney and its excretory apparatus can now be visualized urographically by either one of two methods—that of excretory and that of retrograde pyelography. These methods serve to verify both the preoperative diagnosis and the postoperative results. A quarter of a century ago nothing like this could be done, and the individual who was so unfortunate as to have been born with a malformation of the kidney had to carry it unrecognized to his grave in most instances, or was subjected to operation under a mistaken diagnosis, without relief of symptoms.

The multiplicity of possible anomalies of the kidney and its excretory apparatus, and of its blood and lymphatic supply, I have classified and tabulated elsewhere, and they need not be discussed here.¹

For purposes of this presentation, three groups of cases are to be considered, namely, those in which (1) the malformation is an accidental finding and has not produced symptoms; (2) the anomaly itself is respon-

Presented at a meeting of the Academy of Surgery of Mexico City, Feb. 8, 1944, and the National Cuban Surgical Society, Havana, Feb. 15, 1944.

Received for publication, July 10, 1944.

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sible for painful symptoms; and (3) the anomaly is associated with other advanced pathologic lesions. As a rule most of the cases which come under the eye of the roentgenologist, urologist, or general surgeon are those in Groups 2 and 3, and these constitute the type of case I propose to deal with in this paper. My purpose is to illustrate the importance of making a correct diagnosis of these anomalies before operation, and to show the operative technique employed and the postoperative results obtained.

I cannot emphasize too strongly the value of conservatism in renal surgery, and the ease with which many varieties of conservative operations can be performed on an anomalous kidney, saving an organ of vital importance, which, in the past, has so often been sacrificed for lack of adequate study and proper preoperative diagnosis. These conservative principles of renal surgery have their proper application in many different types of congenital malformations of the kidney, but more especially in those involving the excretory apparatus of the organ. Among these, the most commonly observed are hydronephrosis, double kidney, horseshoe kidney, cysts of the kidney and polycystic kidney, and it is to these varieties of congenital pathologic conditions of the kidney that I shall direct my attention in this presentation.

CONGENITAL HYDRONEPHROSIS

Dilatation of the kidney pelvis for lack of drainage is caused by obstruction at the ureteropelvic junction or anywhere in the course of the ureter, and may be either congenital or acquired.

The modern clinical conception of hydronephrosis was definitely established with the introduction of pyelography, since it then became possible to visualize the kidney, to study its function more accurately, to establish a correct preoperative diagnosis, and to formulate a better prognosis. In the preurographic period most patients with hydronephrosis were submitted to the radical procedure of nephrectomy, but at the present time the tendency is to conserve as much of the renal parenchyma as possible, in an effort to save the kidney. To this end many conservative procedures have been presented from time to time which are actually plastic operations for the orthopedic reconstruction of the renal pelvis, designed to improve drainage, relieve painful symptoms, and overcome infection.³

Albarran⁴ in 1898 was the first to introduce this orthopedic principle, by resecting the lower pole and the pelvis of a hydronephrotic kidney—an operation which was crowned with complete success. Credit for other conservative operations in preurographic days should also be given to Trendelenburg,⁵ Kuster,⁶ Fenger,⁷ Morris,⁸ Israel,⁹ Bazy,¹⁰ Terrier and Boudouin,¹¹ Delbert¹² and others. Thus Fenger applied the Heineke-Mikulicz procedure for pyloric stenosis to the correction of stricture at the ureteropelvic junction, a principle which has since been popularized and modified by many modern writers, among others Young,¹³ von Lichtenberg,¹⁴ Beer and Hyman,¹⁵ Hinman,¹⁶ Leguen,¹⁷ Marion,¹⁸

Papin,¹⁹ Foley,²⁰ Schwyzer,²¹ Quimby,²² Walters and Braasch,²³ Ormond,²⁴ Lubash,²⁵ Moore,²⁶ Gibson,²⁷ Priestley,²⁸ Mathé and De La Peña,²⁹ and others.

However, since the introduction of urographic studies the tendency has been to correct the hydronephrosis by removing the extrinsic or intrinsic cause of the obstruction. The most common causes of congenital hydronephrosis are: stenosis or stricture at the ureteropelvic junction with or without valve or constricted fibrous ring, aberrant polar blood vessels, fibrous bands of adhesions with kinking of the ureter, high insertion of the ureter, and malposition of the kidney. In fact all these causes may be present in the same case, but any one of them is sufficient alone to cause hydronephrosis.

The extrinsic causes are first corrected by a complete nephrolysis and ureterolysis, ligation of small aberrant blood vessels, and section of any fibrous bands of adhesion that may constrict the ureter. For correction of the intrinsic causes the three most usual plastic methods of reconstruction of the renal pelvis are: (1) section and plication of the constricted ureteropelvic junction to relieve mechanical obstruction; (2) resection of the renal pelvis with or without transplantation of the ureter to the most dependent portion of the pelvis, in order to secure good drainage; and (3) lateral anastomosis of the ureter to the renal pelvis by a Y-shaped incision, to enlarge the ureteropelvic outlet.

In the conservative treatment of congenital hydronephrosis it is of paramount importance at the close of the plastic procedure to establish proper drainage by a temporary nephrostomy. This is especially true in the infected type of hydronephrosis. The nephrostomy tube should be introduced through the cortex of the kidney into the most dependent portion of the renal pelvis. It should be accompanied by a ureteral catheter which passes on through the pelvis and into the ureter, thus serving as a splint to hold the ureter straight for the purpose of adequate drainage. This temporary drainage from the renal pelvis may also be obtained by an indwelling ureteral catheter.³⁰

While the procedure of choice in congenital hydronephrosis is a conservative operation, it is obvious that if the kidney is already devoid of function the only recourse is total nephrectomy, provided of course that in the kidney of the opposite side there is a normal pyelogram and evidence of good function. In cases in which the hydronephrosis has not been satisfactorily corrected by the conservative plastic orthopedic procedure, complete relief of symptoms can still be obtained by carrying out a secondary nephrectomy.³¹

In choosing the type of conservative operative procedure for relief of uncomplicated congenital hydronephrosis, I have twice resected a polar accessory blood vessel. In three cases fibrous bands of adhesion causing kinking of the ureter were completely relieved by nephrolysis, ureterolysis, and nephropexy. In two other instances resection of the pelvis of the kidney was carried out to correct hydronephrosis, accompanied by a

temporary nephrostomy, with good success. A pyelo-ureteral anastomosis gave relief in one case of stenosis at the ureteropelvic junction; here, too, a temporary nephrostomy followed and gave good results. In another instance, where there was high implantation of the ureter, section and ligation of the ureter, followed by ureteropelvic anastomosis and temporary nephrostomy, gave complete relief. In another somewhat similar case I carried out resection of the pelvis and ureter, transplanting the latter to the most dependent part of the reconstructed pelvis in order to avoid sectioning an important aberrant blood vessel.

In all these operations for congenital hydronephrosis I have had completely satisfactory results both anatomically and functionally. I have always concluded the procedure with a nephropexy to secure a better position for the kidney and ureter, for purposes of drainage.

The good results obtained in this small series of cases have been due, first, to the careful selection of cases; second, to the use of a rigorous technique; and finally, to the fact that diversion of the urine was carried out in all cases of resection of the renal pelvis and in those of ureteropelvic anastomosis.

All these ten patients had suffered with painful abdominal symptoms over a long period of time, and in every case complete relief of these symptoms as well as of urinary disturbances was obtained.

In other types of congenital hydronephrosis with associated pathology, such as nephrolithiasis, double kidney, or horseshoe kidney, I carried out in two instances a heminephrectomy; in one case a polar resection of the kidney for stones in the upper calyx, with hydronephrosis of that calyx; and in another case the same procedure was applied successfully to a lower calyx.

In another group of hydronephrotic cases with hydro-ureters there was a combination of lesions for which I carried out a combined ureteronephrectomy or ureteroheminephrectomy, the aim in the latter case being to save the half of a double kidney by plastic operation.

Admittedly, the cases that are suitable for conservative operation must be carefully selected. It is obvious that not all cases of congenital hydronephrosis are amenable to conservative surgical procedures. Out of a group of forty cases of marked hydronephrosis that I have studied personally, in eighteen operation was not carried out; in some of the eighteen symptoms were relieved by conservative urological measures, consisting of cystoscopic treatments with dilatation of the ureters, kidney pelvis lavage, and administration of modern urinary antiseptics. However, in most of these cases, the sac of the hydronephrosis was of moderate size, was accompanied by pyelitis and pyelonephritis, and the kidney still had fairly good function as revealed by the urea estimation and phthalein elimination, as well as by urographic studies. Of the group in which operation was not done, seven cases were bilateral.

Of the remaining twenty-two patients, twelve had associated pathology or the kidney was already devoid of function, so that these necessarily

came to total nephrectomy. The other ten cases (25 per cent), therefore, represented the number found suitable for orthopedic reconstruction, by means of some form of conservative plastic procedure for correction of the hydronephrosis.

In all these cases the kidney was exposed by the lumbar route, and complete nephrolysis and ureterolysis were carried out. In some requiring drainage, nephrostomy was instituted and in most instances was maintained for from three to four or six weeks. In all cases nephropexy was performed, to place the kidney and ureter in good position for drainage. Before leaving the hospital, the anatomic and functional results were checked up in every case, in order to verify the final results obtained.

DOUBLE KIDNEY

The need for orthopedic reconstruction of a double kidney is obvious, whenever the pathologic condition in such a kidney is clearly demonstrated in the pyelogram. This is particularly true in cases in which there are persistent painful abdominal symptoms which have paved the way for erroneous diagnosis, and which have not yielded to futile abdominal operations. Whenever careful urographic studies of excretory urograms or of retrograde pyelograms have disclosed the impaired dynamism and faulty mechanics of the double kidney, as the direct cause of the delayed emptying time of the kidney, leading to intermittent crises of hydronephrosis, the malformation plainly demands appropriate surgical treatment for its correction before the complete destruction of the entire renal parenchyma takes place, which will demand total removal of the organ.

In carefully selected cases of double kidney with painful symptoms it appears that some type of conservative operation should be carried out to reconstruct the anomalous organ, thereby providing it with normal function. Here too, as in hydronephrosis, there are several types of plastic procedure which are capable of achieving this end. Among these are (1) anastomosis of the two renal pelves; (2) anastomosis of the upper ureter to the lower renal pelvis; (3) anastomosis of the two ureters at any level; (4) transplantation and reimplantation of one or both ureters; (5) anastomosis of the lower renal pelvis to the bladder in certain cases of ectopic double kidney, and (6) heminephrectomy, or resection of one-half of the double kidney, with or without removal of the corresponding ureter.

Anastomosis of the two renal pelves or of the two ureters has seldom achieved permanent cure, and most of the cases in which it has been employed have unfortunately come sooner or later to secondary nephrectomy. When one is confronted, therefore, with a case of double kidney and double ureter in which an unavailing abdominal operation has been performed, without relief of symptoms, the best prospect of cure lies in carrying out a heminephrectomy.³²

I had the opportunity not so long ago to operate upon a patient with a case of this kind with gratifying results. She was a young woman who had been operated upon elsewhere for chronic appendicitis, but symptoms were not relieved. Upon urographic examination she was found to have an enlarged right double kidney with double renal pelves and ureters. The ureters, after crossing one another, became united above the bladder, resulting in urinary stasis, with marked dilatation at their point of union, as well as pyelectasis and caliectasis. Pyelitis and pyelonephritis were present, along with an appreciable degree of nephroptosis. When medical treatment failed to bring relief, the patient was completely cured by resection of the upper pole of the double kidney and removal of the corresponding ureter, followed by nephropexy of the half of the kidney left in situ, with a view to straightening the ureter and securing good drainage. Three weeks after operation the pyelogram revealed a normally functioning right kidney, thus confirming the success of the orthopedic procedure. The patient has since given birth to a baby without any urinary inconvenience, and is now completely free from symptoms.

Owing to the almost inevitable faulty mechanics of a double kidney, resulting in dynamic dysfunction of the excretory apparatus of the kidney, the emptying time is retarded and the elimination incomplete in one or both pelves of the double organ. This is plainly shown in the delayed urogram taken one or more hours after intravenous injection of the opaque substance, demonstrating the actual surgical pathology present in the double organ.

As the crossing of the two ureters in the double kidney is quite characteristic in this malformation, interfering with the physiologic peristaltic contraction and retarding the emptying time of the renal pelves, we have here essentially the same phenomenon of an extrinsic mechanical factor that we commonly observe in cases of aberrant blood vessels, causing obstruction at the ureteropelvic junction, and resulting here too in hydronephrosis.

For the same reason, therefore, that we remove an aberrant blood vessel for the orthopedic surgical relief of hydronephrosis in a single kidney, we likewise in double kidney do a heminephrectomy with removal of the corresponding ureter, in order to relieve mechanical obstruction and achieve a permanent cure, with complete disappearance of symptoms, whether abdominal or urinary.

HORSESHOE KIDNEY

Among the most important congenital malformations of the kidney, demanding operative intervention, with orthopedic surgical reconstruction of the anomalous organ to relieve painful symptoms, is the classic horseshoe kidney.²³

In the surgical treatment of horseshoe kidney I have elsewhere described four groups of cases which we can now reclassify for practical purposes into five groups as follows:

- Group 1. Silent horseshoe kidney without any painful symptoms.
- Group 2. Horseshoe kidney associated with indefinite abdominal pain, urinary symptoms and gastrointestinal disturbances.
- Group 3. Horseshoe kidney associated with gross pathologic lesions in one-half of the fused organ.
- Group 4. Horseshoe kidney associated with gross pathologic lesions in both renal pelves.
- Group 5. Horseshoe kidney associated with other types of anomalies, such as the presence of three or four renal pelves and ureters.

We are here concerned with the most common type, the cases usually observed clinically, such as those listed in Groups 2 and 3, which demand some form of surgical orthopedic reconstruction to relieve symptoms and bring about a permanent cure.

Although operations for reconstruction of fused kidneys were performed previous to the urographic era, it is only rather recently that they have become popularized. In the past most of the operations performed on the horseshoe kidney were done, not for the anomaly per se, but for the relief of associated pathology in one-half of the double organ, for which such procedures as heminephrectomy, nephrolithotomy, pyelolithotomy, or even ureteropelvic anastomosis has been carried out.

For the orthopedic reconstruction of the anomaly per se, however, in order expressly to relieve painful symptoms for which it alone is responsible, no procedures have been envisaged until rather recently, when Papin,³⁴ Foley,³⁵ Gutierrez,² and others advocated symphysiotomy or division of the renal isthmus as a means of relieving persistent symptoms and providing a definitive cure.

In a typical case in which I recently operated successfully upon the patient, a woman had been suffering for long years with what I have called the horseshoe syndrome, or the horseshoe kidney disease, consisting of indefinite abdominal pain, urinary symptoms and gastrointestinal disturbances. After she had received treatment for chronic cholecystitis, chronic appendicitis, colitis, and other abdominal complaints for many years, to the extreme of becoming practically a neurotic for lack of relief of her symptoms, her condition was finally diagnosed as horseshoe kidney, for which she was referred to me for examination and treatment. The complete urologic and urographic examination disclosed the presence of a horseshoe kidney with pyelitis and pyelonephritis, marked urinary stasis, and evidence of pyelectasis and calyectasis, thus clearly revealing that the patient was suffering with the horseshoe kidney disease.

In this case, after proper preliminary preparation, I carried out an orthopedic reconstruction of the fused organ by an extraperitoneal

symphysiotomy operation, or division of the renal isthmus, followed by nephrolysis, ureterolysis, and right nephropexy.²

The purpose of this orthopedic procedure was, first, to relieve the pressure of the isthmus upon the great abdominal vessels by separating the two kidneys from each other and rotating them outward from their midline position to occupy their normal position, one in each lumbar region, and second, to relieve the mechanical obstruction of the ureters, caused by their ventral position in front of the renal isthmus, which interferes with good drainage.

The postoperative results of this plastic procedure for division of the renal isthmus were truly dramatic. Three weeks after the operation the retrograde pyelograms and the renal functional tests revealed not only that both kidneys were working perfectly and appeared to be in their normal position, but also that the ureters likewise had assumed the correct position and were providing good drainage. The operation for the orthopedic reconstruction of the anomalous organ was thus entirely satisfactory, and the patient was relieved of all symptoms, abdominal and gastrointestinal as well as urinary.

From this case it is possible to see the necessity of recognizing in advance the indications for applying the principles of orthopedic surgical reconstruction in cases of horseshoe kidney associated with the horseshoe kidney syndrome.

In addition to symphysiotomy for division of the renal isthmus, even a symphysiectomy can safely be carried out, if indicated, removing the entire isthmus of the horseshoe organ, as in a case recently reported by Lower,³⁶ when a nephrectomy was successfully performed for removal of a third kidney ensconced in the middle portion of the isthmus of the horseshoe organ.

For cases of horseshoe kidney included in Group 3, in which the anomalous fused organ is accompanied by some gross type of pathologic lesion in one of its halves, several forms of surgical procedure are available. Among the simpler are pyelotomy and nephrotomy for removal of stones, and nephrostomy to provide drainage in pyonephrosis. Among the orthopedic procedures are pelvi-ureteral anastomosis for correction of hydronephrosis, and heminephrectomy for removal of one-half of the horseshoe organ in cases of advanced nephrolithiasis, tuberculosis, or tumor, and also in cases in which one of the halves is devoid of function.

Horseshoe kidney associated with bilateral nephrolithiasis can also be submitted to orthopedic correction, the type of surgical procedure being chosen on the basis of the functional capacity of the respective kidneys that constitute the fused organ. The procedure should be carried out first on the better side, so that, if it becomes necessary, heminephrectomy can be carried out in the kidney of the opposite side.

CONGENITAL CYSTS OF THE KIDNEY

Two distinct types of congenital cysts of the kidney confront the surgeon, namely the large solitary cysts of the kidney and the poly-

cystic kidney. I have presented elsewhere a classification of the many different varieties of cysts of the kidney in a report on ten cases, delivered before the American Urological Association in 1941.³⁷ I have also described the operative technique employed in the orthopedic correction of this cystic type of malformation by suitable resection, and the results obtained thereby.

Both of the two principal types of cystic malformations of the kidney were formerly regarded exclusively as medical entities, and were in fact seldom correctly diagnosed preoperatively. With the advent, however, of the modern means of diagnosis, accuracy in the differentiation of these two entities is now possible, and their orthopedic surgical correction has been made feasible in some cases.

Although this cystic condition is congenital, it is not often recognized until painful abdominal symptoms make their appearance, or until urinary disturbances call for a complete urographic and urologic examination. Large solitary cyst of the kidney is as a rule unilateral, while polycystic kidney is generally bilateral. Both conditions are today, to a certain extent, amenable to conservative surgical correction.

Large Solitary Cyst of the Kidney.—The large solitary cyst of the kidney may be located in any part of the organ. When it is in the upper pole of the right kidney it may easily be mistaken for some other pathologic lesion of the right upper quadrant of the abdomen, and its diagnosis is then difficult unless it is clearly visualized roentgenographically. The renal symptoms may in fact be completely masked by those of the liver and gall bladder, upon which the cyst impinges; hence, these cysts frequently give rise to gastrointestinal manifestations.

These large serous cysts fall anatomicopathologically into two groups: (1) cysts connected with a calyx or the renal pelvis, and (2) cysts that have no such connection. The latter are far more common, and may exist for many years without giving symptoms until they reach an enormous size, sometimes becoming several times the size of the kidney itself. According to the type of their content these renal cysts may be classified as serous, hemorrhagic, purulent, tumor containing, calcified, hydatid, dermoid, or tuberculous. The renal cyst may also be accompanied by hydronephrosis or other type of pathologic condition of the kidney, such as stone, or cancer. Although usually unilateral, the cyst may be found in both kidneys and occupying both poles. In the most common type, however, it is located in the upper or lower pole of one kidney. A cyst may remain silent until its pressure upon surrounding structures results in painful symptoms, chiefly abdominal. As soon as infection sets in, it also causes hematuria and pyuria, giving evidence of pyelitis and pyelonephritis.

The modern tendency in conservative renal surgery is to resect the cyst in order to save the kidney. The procedure will vary with the individual type of case. Obviously when the kidney parenchyma has been

destroyed by compression of the cyst, and the kidney has become functionless, nephrectomy must be carried out. But when the cyst has involved only a limited portion of the parenchyma, a conservative orthopedic operation can still be performed to relieve the organ of its malformation and its painful symptoms. This will consist of removing the cyst and carrying out a complete nephrolysis, ureterolysis, and nephropexy. When the cyst is very large and has destroyed a considerable amount of renal parenchyma, an orthopedic resection of the entire upper or lower pole is called for. When it is connected with a calyx, partial resection including a calycectomy should be carried out, after which the calyx should be sutured to prevent leakage of urine, and the raw surface of the kidney covered with fat to prevent bleeding. Care should of course be taken to see that the blood supply of the remaining portion of the kidney is adequate.

Experience has shown, therefore, that the kidney upon which a large solitary cyst has developed can, in the majority of cases, be definitely corrected by a conservative orthopedic procedure, consisting either of a total resection of the cyst alone, without parenchyma, or of a partial nephrectomy, designed to reconstruct the anomalous organ, to relieve symptoms, and to restore function.

Polycystic Kidney.—Polycystic disease of the kidney is a congenital malformation of the kidney, characterized by formation of multiple cysts of the renal parenchyma. It is generally bilateral and progressive, with a tendency gradually to destroy the kidney parenchyma, diminish renal function, and hasten renal failure. It is quite commonly found in association with surgical pathologic conditions and, in most instances, with pyelitis and pyelonephritis, causing hypertension, and gastrointestinal disorders. In advanced cases the polycystic kidney may be enormously enlarged and may occupy the entire flank on each side of the abdomen. The diagnosis can be definitely made with complete urographic studies, in which the pyelogram will disclose the typical elongation of the calyces, thus serving to confirm the polycystic condition.

The clinical importance of recognizing this entity lies in the fact that whereas in the past polycystic kidney was considered exclusively a medical entity, we know today that the condition can in reality be corrected to some extent by conservative surgery, and the symptoms relieved, thus prolonging life and providing comfort.

Three types of cases must be considered: (1) The polycystic disease is still silent, and gives no symptoms. (2) There are present not only painful abdominal symptoms but also urinary disturbances, the gastroenterorenal syndrome, uremic symptoms, and hypertension. (3) In addition to the symptoms in Group 2, there is also a concomitant pathologic lesion, such as hydronephrosis, stones, tuberculosis, tumor, rupture of a cyst with hemorrhage, or infection of a cyst. All of the cases that give rise to painful symptoms are amenable to relief by conservative surgical measures.

With accuracy in diagnosis and proper preliminary preparation, many of these patients can be operated on successfully today, not only to correct in some degree the congenital malformation, but also to relieve symptoms and prolong what may be a life of comfort by carrying out some type of orthopedic procedure which will restore better function.

Many conservative surgical procedures have been employed for relief of this congenital malformation of the kidney, such as aspiration of cysts, multiple puncture of cysts, renal decapsulation, and resection of cysts. Goldstein³⁸ recently described a method of anchoring the kidney to the skin, after a partial cortical nephrotomy to create a nephrocutaneous fistula, thus facilitating a repetition of the aspirations as often as necessary to relieve the tension of the cysts. Other types of conservative operation, such as nephrolithotomy, pyelolithotomy, and nephrostomy, have also been carried out. Even nephrectomy can be performed, provided there is sufficient function in the kidney of the opposite side.

I have operated successfully upon five patients (my own cases) with polycystic kidney and associated pathology, performing two nephrectomies, one of which was for tumor and the other for persistent bleeding; one with pyelolithotomy, and one with nephrolithotomy; and in one interesting case I operated upon both kidneys for relief of an infected polycystic condition, carrying out a multiple aspiration of cysts and bilateral renal decapsulation.³⁹

In this last case the patient was suffering with advanced uremic symptoms, paralytic ileus, and marked hypertension. The excretory and retrograde pyelographic studies revealed that the left kidney was obviously polycystic in character and of enormous size, occupying the entire left abdomen. The right kidney was practically functionless and the retrograde studies disclosed an atrophic type of polycystic kidney. I operated upon the left kidney first, aspirating multiple small cysts and in addition two large ones containing, respectively, 40 c.c. and 50 c.c. of pus. I then decapsulated the kidney, to which the extraordinarily thick capsule was closely adherent. Six weeks later I operated on the right kidney, aspirating multiple small and large cysts and decapsulating this kidney also. The results were excellent in both operations. The post-operative checkup showed that both kidneys had gained in function and that the patient was entirely free from symptoms.

SUMMARY AND CONCLUSIONS

1. Every anomaly of the kidney is a potential surgical condition.
2. Congenital malformations of the kidney giving symptoms are frequently amenable to surgical orthopedic correction by plastic surgery.
3. Anomalies of the kidney are often responsible for painful abdominal symptoms.
4. Many futile abdominal operations have been performed for symptoms referable to an unsuspected renal anomaly

5. Among the most common unrecognized anomalies of the kidney are congenital hydronephrosis, double kidney, horseshoe kidney, large solitary cyst of the kidney, and polycystic kidney, which are here discussed in detail.

6. Many congenital malformations of the kidney demand conservative surgical intervention to relieve symptoms that are due to the anomaly per se.

7. Orthopedic surgical reconstruction of the malformed kidney has found its definite place in modern urology.

8. When excretory urographic studies reveal the presence of a congenital malformation, the patient should be submitted to a complete urologic examination, including bilateral retrograde pyelograms.

9. Plastic surgery for the correction of renal anomalies should be carried out only in well-selected cases, since it is obviously useless in a kidney already devoid of function.

10. Every patient submitted to orthopedic surgical reconstruction of an anomalous kidney should be checked functionally and urographically before leaving the hospital, in order to ascertain the results obtained.

REFERENCES

1. Gutierrez, R.: The Role of Anomalies of the Kidney and Ureter in the Causation of Surgical Conditions, *J. A. M. A.* 106: 183-189, 1936.
2. Gutierrez, R.: Operative Technique for Division of Renal Isthmus in Horseshoe Kidney, *Ann. J. Surg.* 55: 28-36, 1942.
3. Gutierrez, R.: Anomalies of the Kidney, Hydronephrosis, Movable Kidney, Injuries of the Kidney, in Cabot: *Modern Urology*, ed. 3, vol. 2, chap. II, Philadelphia, 1936, Lea & Febiger, pp. 374-509.
4. Albarran, J.: Cas de résection autoplastique du rein pour parer à une rétention rénale partielle, *Bull. Acad. de méd.* 40: 59, 1898.
- Albarran, J.: Résection orthopédique du rein: *Médecine Opératoire des Voies Urinaires*, Paris, 1909, Masson & Cie, p. 231.
- Albarran, J.: Cinq observations d'anastomoses latérales de l'uretère et trois observations de résections orthopédiques du rein; quoted by Gardner, F.: *Opérations plastiques et anastomoses dans le traitement des rétentions du rein*, Paris Thésis, 1903, pp. 189, 191, 194.
5. Trendelenburg, F.: Nephrectomie bei Nierengeschwülsten. *Niederrheinische Gesellschaft für Natur- und Heilkunde zu Bonn. Sitzung von 23 No. 1885*, *Berl. klin. Wehnschr.* 23: 540, 1886.
6. Kuster, Ernst: Surgery of the Kidneys, *Deutsche Chirurgie*, Lief., pp. 506-7, 1896-1902.
7. Fenger, C.: Operation for the Relief of Valve Formation and Stricture of the Ureter in Hydronephrosis or Pyonephrosis, *J. A. M. A.* 22: 335-343, 1894.
8. Morris, Henry: *Surgical Diseases of the Kidney and Ureter*, ed. 2, vol. II. Cassell & Co., Ltd. London, 1901, p. 220.
9. Israel, J.: Beiträge zur Ureterchirurgie, *Zentralbl. f. Chir.* 16: 490, 1899.
10. Bazy, P.: Hydronephrose, *Encycl. Franç. d'Urol.*, Octave Doin et Fils, Paris 3: 150, 1914.
11. Terrier, F., and Boudouin, M.: De l'Hydronephrose Intermittente, *Rev. de chir.* 2: 719, 833, 1055, 1891.
12. Delbert, P.: Urétéro-pyelostomie, *Gaz. d. hôp.* 71: 1379, 1898.
13. Young, H. H.: Obstructions of the Ureter Produced by Aberrant Blood Vessels; a Plastic Repair Without Ligation of Vessels or Transplantation of Ureters, *Surg. Gynec. & Obst.* 54: 26-38, 1932.
14. Von Lichtenberg, A.: Plastic Surgery of the Renal Pelvis and Ureter, *J. A. M. A.* 93: 1706, 1929.
15. Beer, E., and Hyman, A.: *Diseases of the Urinary Tract in Children*, New York, 1930, Paul B. Hoeber, Inc.

16. Hinman, Frank: The Pathogenesis of Hydronephrosis, Surg., Gynec. & Obst. 58: 356-376, 1934.
17. Legueu, F.: A propos des opérations conservatrices dans les rétentions rénales. XIIIe Congrès International de Médecine, Paris, Chir. Urin. 11: 44, 1900.
Legueu, F., Fey, B., and Truchot, P.: La motricité normale et pathologique du bassin. Son exploration par la pyéloscopie, Bull. Soc. franç. d'urolog. 201-207, 1924.
- Fey, B.: Les rétentions pyéliquies fonctionnelles, Arch. Urol. de la Clin. de Necker 5: 93, 1925.
18. Marion, G.: Hydronephrose, Traité d'Urologie, Paris, 1935, Masson & Cie, pp. 468-483.
Marion, G.: Etiologie et Traitement des Hydronephroses, Madrid, 1930. Congres. Internationale d'Urologie.
19. Papin, E.: Les hydronephroses, Paris, 1930, Octave Doin et Cie.
Papin, E.: Chirurgie du Rein, Paris, 1928, Octave Doin et Cie.
20. Foley, F. E. B.: A New Plastic Operation for Stricture at the Uretero-pelvic Junction, J. Urol. 38: 643-672, 1937.
21. Schwyzer, A.: New Pyelo-ureteral Plastic for Hydronephrosis, S. Clin. North America 3: 1440-1441, 1923.
22. Quinby, W.: Factors Influencing the Operative Procedure in Hydronephrosis, J. A. M. A. 93: 1709, 1929.
23. Walters, W., and Braasch, W. F.: Urinary Obstruction and Hydronephrosis: Resection of the Renal Pelvis, the Kidney and the Ureter: Report of Nine Cases, J. A. M. A. 93: 1710-1716, 1929.
Walters, W.: Resections of the Renal Pelvis and Other Plastic Operations for Hydronephrosis, Surg., Gynec., & Obst. 85: 508, 1932.
24. Ormond, J. K.: End-results of Plastic Operations on the Kidney Pelvis for Hydronephrosis, Am. J. Surg. 38: 70-79, 1937.
25. Lubash, S.: Uretero-pyeloneostomy for Hydronephrosis: A New Operative Technique, J. Urol. 34: 222-229, 1935.
26. Moore, T. D.: The Diagnosis and Management of Hydronephrosis Secondary to Ureteropelvic Obstruction of the Noncalculous Type, Am. J. Surg. 38: 101-115, 1937.
27. Gibson, Thomas E.: Hydronephrosis: Standardization of Surgical Treatment, New England J. Med. 222: 910-917, 1940.
28. Priestley, J. T.: The Conservative Surgical Treatment of Non-calculous Hydronephrosis, Surg., Gynec. & Obst. 68: 832-841, 1939.
29. Mathé, C. P., and De La Peña, E.: Surgical Repair of Hydronephrosis With Reference to Technical Points Favoring Relief, J. Urol. 21: 21, 1934.
30. Gutierrez, R.: The Value of the Indwelling Ureteral Catheter in Urinary Surgery, Surg., Gynec. & Obst. 50: 441-454, 1930.
31. Gutierrez, R.: Nephrostomy as a Preliminary Drainage in Preparation for Secondary Nephrectomy, J. Urol. 31: 305-362, 1934.
32. Gutierrez, R.: Double Kidney as a Source of Impaired Dynamism. Its Surgical Treatment by Heminephrectomy, Am. J. Surg. 65: 256-267, 1944.
33. Gutierrez, R.: The Clinical Management of Horseshoe Kidney, New York, 1934, Paul B. Hoeber, Inc.
34. Papin, Edmond: Foreword to Gutierrez, Robert: The Clinical Management of Horseshoe Kidney, New York, 1934, Paul B. Hoeber, Inc.
35. Foley, F. E. B.: The Surgical Correction of Horseshoe Kidney, J. A. M. A. 115: 1945-1951, 1940.
36. Lower, W. E.: The Problem of the Fused Kidney, J. Urol. 35: 588-595, 1936.
37. Gutierrez, R.: Large Solitary Cysts of the Kidney; Types, Differential Diagnosis and Surgical Treatment, Arch. Surg. 44: 279-318, 1942.
38. Goldstein, A. E.: A New Surgical Procedure for Treatment of Polycystic Kidneys, J. Urol. 34: 536-547, 1935.
39. Gutierrez, R.: Secondary Pathological Changes in Polycystic Kidney Disease, Discussion, J. Urol. 50: 148-150, 1943.

EXTENSIVE VARICOSITIES OF THE LEG ORIGINATING FROM THE GLUTEAL VEIN

REPORT OF A CASE

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THE case herewith reported is of interest because the very extensive varicosities of the right leg originated from the inferior gluteal vein. This vein is a tributary of the internal iliac, whereas the saphenous vein, which is involved in almost all cases of varicosities of the legs, is a



Fig. 1 —Photograph taken Feb. 9, 1940

tributary of the external iliac through the femoral. In a review of the recent literature there was found no mention of varicosities of gluteal origin. The history of this case strongly indicates that the condition was of developmental origin.

Received for publication, July 3, 1944.

CASE REPORT

CASE 1 (REPORT No. 31936).—O. B., a 37-year-old white man working as a carpenter, was admitted to the Riverside Infirmary Feb. 9, 1940. He had been aware of large veins in the right leg since childhood. He recalled having had, at the age of 10 to 12 years, ulcers which were slow in healing. For many years he had worn tightly laced knee boots constantly in order to support the leg. His general health had been good. He was well developed and well nourished. Examination revealed no finding



Fig. 2.—Feb. 9, 1940, point pressure over inferior gluteal vein after emptying veins by elevating the leg.

of note other than that pertaining to the right leg. Fig. 1 adequately portrays the extensive varicose veins on the posterolateral aspect of the thigh and the lower leg. There was no appreciable involvement on the medial aspect, however the great saphenous vein was readily palpable in the lower thigh. The varicosities were easily emptied by elevating the leg (Fig. 2). When empty, point pressure applied over a large vein in the lower gluteal region prevented their rapid filling upon the patient's standing. Release of the pressure resulted in rapid filling from above downward. A diagnosis was made of varicose veins originating from the inferior gluteal vein.

Feb. 10, 1940, operation was performed under nitrous oxide anesthesia. An incision was made over the large bulbous varicosity in the inferior gluteal region. The vein was isolated, severed, and its upper segment dissected to its point of disap-

pearance into the gluteal muscle. An attempt at stripping the distal segment met with failure due to its thin wall and adherence to the skin. A ureteral catheter was passed into it downward for two-thirds the length of the thigh, and 10 c.c. of 5 per cent sodium morrhuate were injected during the withdrawal. The ends of the vein were ligated with plain catgut and the skin edges approximated with clips. A moderately large vein situated several centimeters anterior and inferior to the main trunk was isolated by dissection, severed, and its ends ligated. An elastoplast bandage was placed from the toes to the knee. Considerable phlebothrombosis followed this procedure, however there was no general swelling of the leg. During the next few

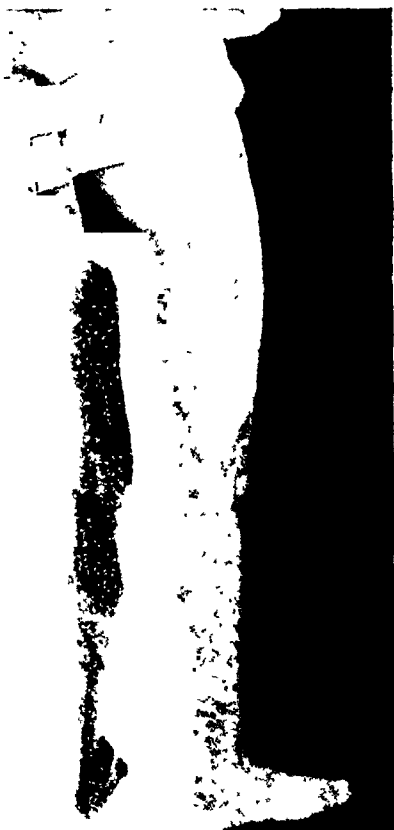


Fig. 3.—April 3, 1941, after treatment.

months, at intervals of one to several weeks, some of the remaining patent varicosities were injected with sodium morrhuate. The patient was last examined Feb. 2, 1943. He had been working steadily. There was no swelling of the right leg or foot, and he complained of no symptoms. There were several moderate-sized varicosities on the lateral aspect of the lower leg.

A NEW HEMOSTATIC CLAMP

DESCRIPTION OF A HEMOSTAT CARRYING MULTIPLE PREFORMED LIGATURES

GONZALO CUBERO O., M.D., SAN JOSÉ, COSTA RICA

SINCE the control of hemorrhage is essential in any operation, any procedure which will facilitate it is worth while. In the present communication is described an ingenious new hemostatic clamp, which through a particular modification can hold one or more ligatures with a special knot, which will be described, already prepared so that they can be tied at the same time that the clamp grasps the bleeding vessel. With this instrument one is enabled to place rapidly and consecutively one or more ligatures without the necessity of an additional maneuver except for the clamping of the bleeding vessel and the necessary traction on the suture ends to fix it.

The clamp resembles a péan forceps (Fig. 1). The lower arm has practically no modification; the upper arm is curved between the joint and the grasping end with dentations on its undersurface; and there extends distally from the region of the joint an additional short arm, which has the form of a half-cylinder that serves to hold the loop of the ligatures. On the opposite end situated above the thumb grasp is a transverse bar constructed like an automobile spring between the leaves of which the free ends of the ligatures are wedged in alternate succession. This provides immediate access to the ends, which can be freed separately and readily by the assistant who simply detaches them and closes the knot while the operator releases the clamp from the grasped vessel. The clamp can be loaded under aseptic conditions by the suture nurse prior to the operation. Consequently, one may have any number of previously prepared ligatures in triplicate amount depending upon the number of clamps so prepared and needed.

Knot.—The knot is an old one which is frequently used except in medicine. It is the double-hitch knot (Fig. 2) and consists of two loops made clockwise (Fig. 3) with the second placed back of the first (Figs. 4, 5, and 6).

Technique of Usage.—Following the incision the operator takes one of these clamps and seizes the bleeding vessels while his assistant by detaching the free ends of the ligature from the special holder simply exerts traction, thereby closing the loop and securing the vessel, the loop being automatically detached from its tilelike ridge by this maneuver. The nature of this loop is such that when it is drawn taut about the vessel it fixes it in such a manner that it cannot slip, and the application of a second knot is unnecessary. Subsequently, all that is necessary is to sever the free ends above the knot. In this manner, by use of the same instrument, the surgeon simply repeats the instrument application and is able to ligate three bleeding points in rapid succession.

Advantages.—The advantages of this clamp are:

1. It reduces the operating time considerably and prevents fatigue on the part of the surgeon.
2. The double loop provides a ligature which is much stronger than the average tie.

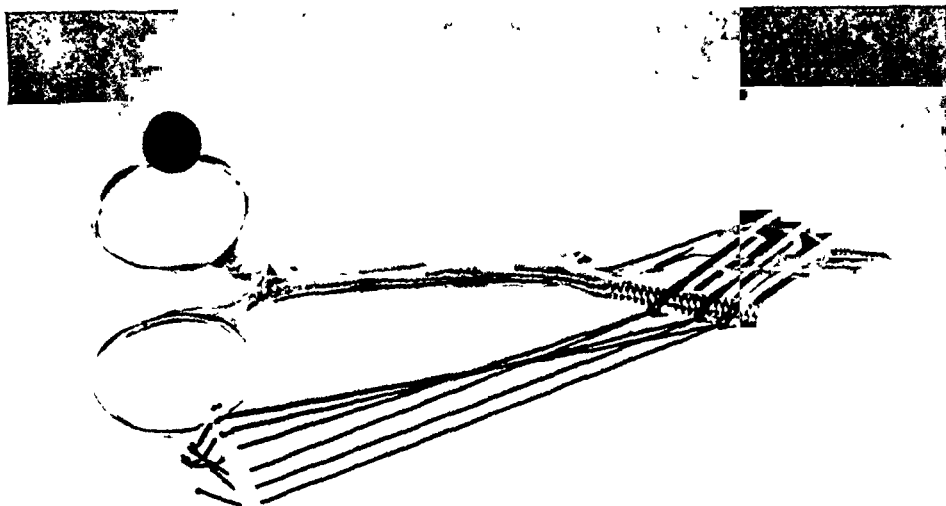


Fig. 1.—Photograph of the hemostatic clamp loaded with three ligatures. The upper arm (lower jaw) is curved between the joint and the grasping end and has dentations on its upper surface. Extending distally from the region of the joint on the upper arm is an additional short arm, which has the form of a half-cylinder which serves to hold the loop of ligatures.

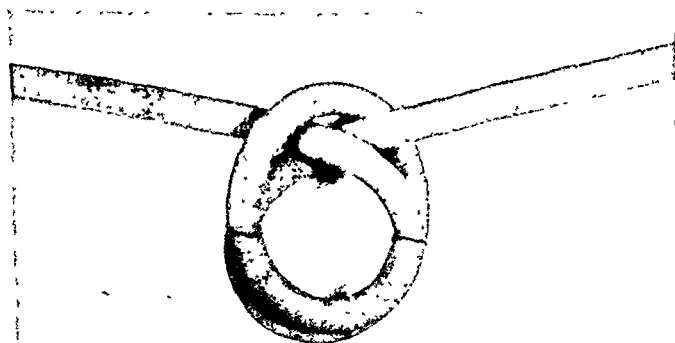


Fig. 2.—Double-hitch knot which is used for the ligatures.

3. The surgeon may concentrate his observation and vision upon the detail of clamping the vessel and is not distracted from the operative field by having alternately to grasp a vessel and then apply a ligature. In a like manner the assistant devotes his attention simply to securing the knot and cutting the free ends, thus obviating at least two manual procedures which are necessary in the conventional application of clamp and ligature.



Fig. 3.—The first step in the making of the double-hitch knot. A clockwise loop is made and held in the left hand; another clockwise loop is made and held in the right hand.



Fig. 4.—Two loops are placed together, placing the second loop back of the first.



Fig. 5.—The completed double-hitch knot.

4. Since the loop is previously prepared, no knot has to be tied, which is always time-consuming and at times difficult because of the tendency of the ligatures to adhere to the wet gloved fingers.

5. *On the battle front or in emergency stations or outpatient clinics* where no physician is available immediately, any attendant may control bleeding vessels rapidly by means of this clamp, which has been loaded

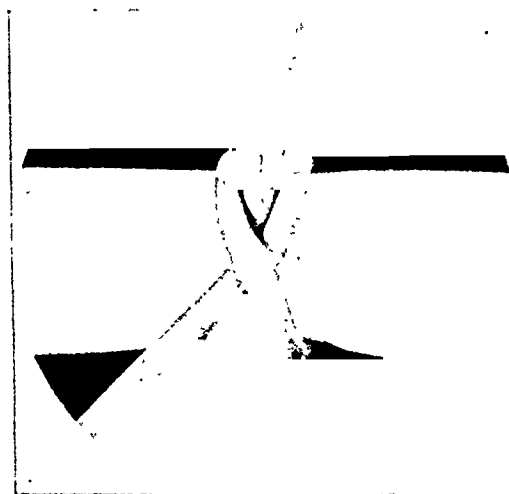


Fig. 6.—The double-hitch knot viewed from above showing the manner in which the knot is held.

previously and sterilized and kept under aseptic conditions, without the necessity even of washing his hands since the loop can be applied without contamination.

6. The loop can be made easily by performing two loops in a clockwise manner, the second loop being placed behind the first.

7. A long-handle model mounting a single loop is invaluable in the ligation of bleeding vessels which must be grasped through a small aperture and secured at a great depth.

Review of Recent Meetings

FIFTY-SECOND ANNUAL MEETING OF THE WESTERN SURGICAL ASSOCIATION

CHICAGO, ILL., DEC. 1 AND 2, 1944

HERBERT H. DAVIS, M.D., OMAHA, NEBR.

1. **Madura Foot**, Francis E. Clough, San Bernardino, Calif.—Madura foot disease does not occur just in the tropics. Forty-eight cases have been reported in the United States. There is no specific treatment. Amputation is often necessary.

2. **The Technic for Closure of the Ring of Post-Operative Abdominal Hernia**, Neil J. Maclean, Winnipeg, Man., Canada.—In the upper abdomen the strong lateral pull of the abdominal muscles causes the hernia ring to have the long diameter transversely, therefore, closure should be done transversely. In the lower abdomen, however, the long diameter is usually vertical, therefore, the closure should be vertical. For the closure of the umbilical hernia Dr. Maclean advised the three-flap method.

3. **Interscapulo-Thoracic Disarticulation of the Arm**, Jacob K. Berman, Indianapolis, Ind.—Disarticulation of the arm is being revived. Main indications are malignant tumors, sarcoma of bone, carcinoma with axillary metastases, and, occasionally, cases of severe trauma. The technique of the operation was described.

4. **Postoperative Deaths**, Erwin R. Schmidt and (by invitation) Ralph M. Waters and Noel Gillespie, Madison, Wis.—This report was based on the records of deaths in 56,000 cases. Deaths on the operating table were due to cardiac conditions, hemorrhage, or anesthesia. Those in the first twenty-four hours following operation were mainly circulatory or central nervous system failures. Those deaths occurring later were mainly due to infection and emboli.

5. **The Use of Thiouracil in the Treatment of Hyperthyroidism**, Arnold S. Jackson, Madison, Wis.—A study of thirty cases was reported. Indications were: iodine-resistant cases, advanced toxic adenoma, adenoma with complications, severe exophthalmic goiter in very young, very old, or debilitated patients, exophthalmic goiter with pregnancy or other diseases, iodine-fast hyperthyroidism, and recurrent or persistent hyperthyroidism. No definite conclusions were given; however, the opinion was expressed that use of thiouracil would not supplement surgery in exophthalmic goiter, but that it will be a valuable adjunct in the treatment of primary or secondary hyperthyroidism.

From the literature Jackson reported that at least seven cases of fatal agranulocytosis have occurred following its use.

6. **Thyroidectomy by the Off the Trachea Method**, Martin C. Lindem, Salt Lake City, Utah.—Lindem advised removing the thyroid by first cutting through the isthmus, then dissecting the lobe from the trachea. In this procedure he feels that there is less danger of injuring the recurrent laryngeal nerves, or the parathyroids, and that much better exposure of the superior thyroid poles can be obtained.

7. **Amino Acids Used Intravenously in Surgical Patients**, Herbert H. Davis, Omaha, Nebr.—The importance of giving protein following operation was stressed. The results of giving intravenous protein digest to 203 surgical patients were given, showing, clinically, a very much improved general condition. There were no serious reactions. Minor reactions occurred in 3 per cent of the injections.

8. **The Use of Skin Flaps in the Repair of Scarred or Ulcerative Defects Over Bone and Tendons**, Earl C. Padgett and (by invitation) John H. Gaskins, Kansas City, Mo.—Ninety-seven cases were reported with the use of skin grafts. They are for the repair of defects over bones and tendons.

9. **The Origin and Growth of an Adenoma of the Islands of Langerhans**, Louis P. Good, Texarkana, Texas.—In a very thorough histopathologic study it was concluded that an adenoma of the islands of Langerhans arises as a result of proliferation of the duct epithelium.

10. **Resection of Pancreas for Hyperinsulinism**, Stanley R. Maxeiner, Minneapolis, Minn., and (by invitation) Colonel Harry E. Bundy.—A case was reported of a discharged soldier, aged 24 years, with typical symptoms, blood sugar going as low as 28 mg. per 100 c.c. At operation 75 per cent of pancreas was removed. There were eight islet tumors. Since the operation the symptoms have been relieved; the blood sugar is stabilized near 100 mg. per 100 c.c.

11. **Resection of the Duodenum and Head of the Pancreas for Carcinoma**, Warren H. Cole and (by invitation) John Reynolds, Chicago, Ill.—Five cases were reported, with one death. One of the four patients still has a pancreatic fistula, and the other three are in good condition. These authors use long loop jejunum, anticipating that they may, at some time, anastomose the pancreas to the jejunum, and place a drain to the region of the pancreas. None of the patients had ascending cholangitis. They feel that the danger of this is lessened by anastomosing the common duct to the jejunum, rather than anastomosing the gall bladder, and that the anastomosis should be made proximal to the anastomosis between the stomach and the jejunum so that the stomach content does not flow over the area.

12. **Pancreaticoduodenectomy for Carcinoma of the Ampulla**, Thomas G. Orr, Kansas City, Kan.—There have been 105 cases of pancreaticoduodenectomy previously reported, including nine cases which Orr reported. Great care should be taken to be sure that the diagnosis is carcinoma. If in doubt, open the duodenum and get biopsy.

The choice of whether to do this procedure in one or two stages should depend upon the condition of the patient. In selecting a technique, one should be adopted which can be done in the shortest time. Enough tissue should be removed and the bile duct used rather than the gall bladder in making anastomosis. Orr believes in restoring the physiology of digestion, by anastomosing the pancreas to the bowel.

13. **Gastric Resection for Certain Acute Perforated Lesions of the Stomach and Duodenum With Diffuse Soiling of the Peritoneal Cavity**, J. Dewey Bisgard, Omaha, Nebr.—Six cases of perforation of the stomach with soiling of the peritoneal cavity were reported in which a gastric resection was done without a fatality. They were all done on men varying from 26 to 62 years of age. Two operations were for carcinoma and four were for ulcers. One of the patients with carcinoma lived twenty months, and the other, three months following operation, dying later from the carcinoma. The four patients with benign ulcer are alive and in good condition.

14. **Surgical Treatment of Pharyngo (Esophageal) Diverticulum** Review of 140 Cases, **Stuart W. Harrington**, Rochester, Minn.—So-called esophageal diverticula really originate in the hypopharynx. A discussion of the one- and two-stage excision of the diverticulum was given, and relative merits evaluated. Harrington favors one-stage operation. He reported 140 cases, 25 of whom were treated by the two-stage operation, with 1 death, and 115 with one-stage operation, in which there were no deaths.

15. **A Review of One Hundred Subtotal Gastrectomies for Benign Ulcers**, **Robert L. Sanders**, Memphis, Tenn.—It was pointed out that there was a changing attitude favoring earlier surgical approach to gastric ulcers. In Sanders' series, 22 per cent of the gastric ulcers were carcinoma. He stated that even carcinoma will partially heal over for a short time with medical treatment. In high resections he does an anticolic anastomosis. Routinely, he removes 55 to 60 per cent of the stomach. He stated that there is likely to be nutritional disturbances if more is removed. Since 1940 he has not done a single pyloroplasty. The operative mortality was 3 per cent. When the duodenal ulcer is firmly adherent to the pancreas, he cuts the duodenum across proximal to this, and inserts his finger in the open end as a guide in the dissection.

16. **Gastro-Jejuno-Colic Fistula**, **Henry K. Ransom**, Ann Arbor, Mich.—The treatment for fistula is necessarily surgical, but the poor condition of the patient and the severe inflammatory reaction about the lesion has been responsible for a high mortality rate. During the years 1934 to 1944, at the University of Michigan Hospital, forty-seven patients with jejunal ulcers were operated upon. Of these, eight had gastro-jejuno-colic fistulas. Ages varied from 31 to 72, the average being 49 years. All but one of the patients were men. The original operation was always a posterior gastroenterostomy.

Two different types of operation were used: I. Radical with gastric resection; II. conservative without radical resection, restoration of the bowel with a typical closure. Fourteen operations were done with two deaths, or 14.3 per cent mortality. One of the deaths was due to a leak resulting in peritonitis, the other to empyema from rupture of a lung abscess.

17. **Surgical Management of Sigmoidal Carcinoma Involving the Urinary Bladder**. Review of Sixty-Four Cases, **Claude E. Dixon** and (by invitation) **Raymond E. Benson**, Rochester, Minn.—Sixty-four cases were reported, 40 patients with extensive resections, and twenty-four with metastases; resection was not done. In the forty resections there were seven deaths. It is advisable to treat these lesions radically, as they often do not metastasize early. The operation consists of removal of part of the bladder with the tumor and an end-to-end anastomosis of the colon.

18. **Preservation of the Sphincters and Intestinal Continuity in Operation for Carcinoma of the Rectal Ampulla**, **Owen H. Wangenstein**, Minneapolis, Minn.—Resection with primary anastomosis, and without an external decompressive vent, is done routinely in Wangenstein's clinic for all unobstructed lesions of the colon demanding partial excision. Carcinoma of the rectosigmoid juncture is treated in the same manner. Such procedures can be accomplished with low risk. In suitable instances of carcinoma of the rectal ampulla, the lesion lying 5 cm. or more above the pectinate line, it is possible to preserve the sphincters and effect a satisfactory removal of the segment of the rectum involved with its lymphatic drainage area. A small perineal incision is made for drainage. Function is usually good.

19. **Peripheral Nerve Injury in Association With Fractures of Long Bones**, **Charles G. Johnston** and (by invitation) **E. S. Gurdjian**, Detroit, Mich.—A series

of sixty-five operated cases of nerve injury in association with fractures of long bones is analyzed. He discussed advisability of neurolysis for the excision of a neuroma with end to end suture of the nerve.

20. Repair of Peripheral Nerves in the Presence of Extensive Soft Tissue and Bone Injuries of the Extremities, Loyal Davis and (by invitation) George Perret and Walter Carroll, Chicago, Ill.—If there is a contamination the authors advise introducing sulfathiazole jelly into the depth of the wound at the time of operation. In case of loss of nerve substance where the nerves cannot be brought together, the use of grafts has a definite place. Autogenous grafts of the same size are best. Later it is often necessary to resect and resuture the distal ends as the nerve fibers cannot get through the scar. Nerve graft banks are in the process of development. Cable grafts are not advised. If autogenous grafts are not available, fresh homogenous grafts may be used.

In severe injuries of nerves, the reaction to the injury may extend both ways in the nerve, proximally as well as distally, therefore, it is often necessary to resect the portion of the nerve proximal to the injury. This point has often been neglected.

21. Chronic Sclerosing Osteitis: Differential Diagnosis, Henry W. Meyerding, Rochester, Minn.—Meyerding reviewed a series of cases seen at the Mayo Clinic in a period of thirty-two years from 1912 to 1943, inclusive. He discussed the symptoms, differential diagnosis, and treatment, which is surgical excision. The results were excellent.

22. The Treatment of Infected Pin Operations for Fracture of the Neck of the Femur, Kellogg Speed, Chicago, Ill.—Onset is usually insidious and not alarming. Attempts at renailing may unhappily be made; usually the fixation agent is finally withdrawn and little else is done. The patient drifts into a condition of chronic osteomyelitis with bed confinement, discharging sinuses, dislocation of the hip, loss of weight, and strength, and may die from the effects or general sepsis. The ilium and acetabulum may become infected and necrotic.

Treatment consists in early recognition, prompt, adequate drainage, and fixation in plaster. Sulfonamide drugs and penicillin may be used if applied wisely. When the head of the femur dies its removal is imperative before the condition can be overcome.

23. Status of the Bone Graft in Ununited Fractures of the Neck of the Femur, Melvin S. Henderson, Rochester, Minn.—In a certain percentage of cases, unfortunately not high, the bone graft can be used. The fibula may be used as a peg, without exposing the joint, by drilling a channel through the trochanter and neck, well into the head. A guide wire and a special drill are used. Results were excellent in twelve of fifteen cases, that is in 88 per cent. A double spica cast is applied. The patient is kept quiet from one to three months.

24. Personal Evaluation of Vitallium Cup Arthroplasty of the Hip Joint, Glen Evan Cheley, Denver, Colo.—Cheley had this operation performed upon himself. He discussed the course of the disease, and his pre- and postoperative treatment and results.

Notices

BARUCH COMMITTEE ON PHYSICAL MEDICINE

The Administrative Board of the Baruch Committee on Physical Medicine has announced the granting of an additional total sum of \$185,000, which is being given by Mr. Bernard M. Baruch for the further advancement of the program in physical medicine and the physical rehabilitation of those disabled in the war. This sum has been divided into seven grants as follows: \$50,000 to the Massachusetts Institute of Technology, Cambridge, Mass.; \$40,000 to the Medical School of the University of Minnesota, Minneapolis, Minn.; \$30,000 to the Medical School of Harvard University, Boston, Mass.; \$30,000 to the Medical School of the University of Southern California, Los Angeles, Calif.; \$15,000 to the Medical School of the University of Iowa, Iowa City, Iowa; \$15,000 to the Medical School of the University of Illinois, Chicago, Ill.; \$5,000 to Marquette University Medical School, Milwaukee, Wis.

The grants to Massachusetts Institute of Technology and the University of Minnesota are in addition to the gift of \$1,100,000 made by Mr. Baruch in April, 1944, at which time grants were made to Columbia University College of Physicians and Surgeons, New York University College of Medicine, the Medical College of Virginia, and for minor research and fellowship programs for the advancement of physical medicine.

The present gift to Massachusetts Institute of Technology is in support of a five-year program of training and research in electronics, instrumentation, and physics in relation to medicine, to be carried on under the auspices of the Department of biology and biological engineering. It was the conviction of the Scientific Advisory Committee of the Baruch Committee on Physical Medicine that Baruch Fellows and other physicians should have more than a superficial knowledge of the physics and technology underlying the physical methods and instrumentation used in this field and it was suggested that training in this aspect might effectively be centered at the Massachusetts Institute of Technology. The program will be under the general supervision of Dr. Francis O. Schmitt, head of the department of biology and biological engineering, and under immediate supervision of Dr. K. S. Lion, assistant professor of applied biophysics, who is an expert in physical instrumentation.

The grant of \$40,000 to the University of Minnesota is to support the development of a three-year teaching and fellowship program in physical medicine. The primary objective of the program is to be the furtherance of fundamental training of research workers and teachers. The program has as its basis the development of scientists in the field of physical medicine. As an auxiliary to this basic training will be developed facilities for the training of clinicians and technicians.

The other grants have been allocated from the fund of \$200,000 given by Mr. Baruch in April. The sum of \$30,000 was granted to Harvard University Medical School for establishment of a three-year program to provide fellowship or residencies to be used for the benefit of qualified physicians who are selected to be trained in this field. This sum will be administered by a strong standing committee on physical medicine, recently appointed by Dean C. Sidney Burwell of the Harvard Medical School, composed of Dr. J. B. Ayer, Dr. D. Denny-Brown, Dr. W. T. Green, Dr. J. H. Means, Dr. A. L. Watkins, and Dr. E. M. Landis (chairman). Appointments to the fellowships, which generally carry stipends of \$2,500, will be

made annually but may be renewed to provide up to three years of specialized study and research. Emphasis will be placed upon training a few men in basic research and clinical investigation.

Unusual opportunities for clinical experience and research in the psychologic and psychiatric aspects of physical medicine will be available at Harvard. The first year will be wholly or in part devoted to basic research related to physical medicine in one of the preclinical sciences such as physiology, anatomy, or biophysics. The second year will be spent in clinical training in physical medicine at the Massachusetts General Hospital and other hospitals affiliated with the Harvard Medical School. In the third year, fellows will be assistants in physical medicine with clinical responsibilities. For candidates with extensive previous training, one-year clinical fellowships will also be granted. Applicants must have an M.D. degree from an approved medical school and a minimum of one year of internship in an approved hospital. Applications may be obtained from the Dean, Harvard Medical School, 25 Shattuck Street, Boston 15, Mass.

The sum of \$30,000 is being granted to the University of Southern California to inaugurate a program of teaching and research in physical medicine in its medical school. The sum of \$15,000 is granted to the University of Illinois to inaugurate a teaching program in physical medicine at its medical school. The sum of \$15,000 is being granted to the Medical School of the University of Iowa to assist in a joint research and teaching program concerning the effectiveness of different methods of applying heat to the deep tissues of the human body. Finally, the sum of \$5,000 is being granted to the Medical School of Marquette University, Milwaukee, Wis., for continuance of research in the physiology and pathology of nerves and muscles as related to physical medicine.

In discussing these grants Dr. Frank H. Krusen, the director of the Baruch Committee, pointed out that Mr. Baruch had been particularly interested in the important field of electronics as applied to medicine and he said that the center at Massachusetts Institute of Technology gave promise of revolutionizing the application of electronics in the diagnosis and treatment of the sick. Dr. Krusen expressed gratitude concerning the establishment of fellowships in physical medicine at Harvard and mentioned the advantage to the field of physical medicine in having this great center assume leadership in the training of fellows. He also stated that the aid given to the University of Minnesota and the University of Southern California would extend the activities of the Baruch Committee into the Midwest and Far West and thus tend to strengthen this important program. In conclusion, Dr. Krusen announced that the Administrative Board does not contemplate the recommendation of any further large grants for the establishment of additional departments of physical medicine in our medical schools. He said that the Baruch Committee would now turn its main attention toward the adequate development of the centers already established, toward providing advice in the organization of proper teaching of physical medicine in medical schools, and, through its strong Committee on War and Postwar Physical Rehabilitation and Reconditioning, would attempt to promote proper development of physical medicine in the rehabilitation and reconditioning of both military and civilian casualties of war. The Board agreed that Mr. Baruch's gifts had served as a means of providing prompt coordination of the entire program for rehabilitation of our wounded and for the provision of the trained personnel so greatly needed in activating this program.

gest that the remote results in duodenal ulcer after gastrojejunostomy are within 10 per cent of being as good as those following gastric resection. Their reported incidence of gastrojejunal ulcer after gastrojejunostomy is 25.9 per cent.

Inasmuch as the authors express a preference for the small gastric resection over more extensive resections, it is not surprising that they are disappointed over the failure of gastric resections to protect against recurrent ulcer. They stress the importance of removing the pylorus and antrum but fail to indicate the length of the afferent duodenojejunal loop, an item of some considerable importance apparently in determining whether recurrent ulcer will follow gastric resection. Though many will not agree with the authors in their reawakening of interest in gastrojejunostomy as a suitable operation for duodenal ulcer, everyone who has an interest in the ulcer problem will find study of the tabular data profitable and interesting.

The authors favor gastric resection over gastrojejunostomy for the following conditions: (1) Gastric or duodenal ulcer complicated by hemorrhage, (2) gastric ulcer, and (3) recurrent ulcer. They are not in complete accord with recent expressions from surgeons suggesting that resection should be undertaken more frequently for gastric ulcer, if only in the interests of resolving the confusion which may exist between ulcer and cancer. On this score, the authors appear to have had more success than others in differentiating ulcer from cancer. They find the presence of a good response to the histamine test a better differential than the x-rays. As a matter of fact, they believe that gastric analysis constitutes an agency almost infallible in diagnostic accuracy in distinguishing between gastric ulcer and cancer (page 26). Very few, if any, who have studied this question critically will be able to subscribe to this thesis of the authors.

SURGERY

VOL. 17

FEBRUARY, 1945

No. 2

Original Communications

Symposium on Thrombo-Embolism

THE PROBLEM OF THROMBO-EMBOLISM

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THE formation and propagation of thrombi in the vascular tree confronts one with many questions. The literature on this subject is very extensive; we have annually reviewed it elsewhere.¹ The purpose of this communication is to describe briefly the methods of diagnosis and treatment which have been gradually developed as a result of our own experience. This discussion will be limited to the peripheral venous system and the pulmonary arterial tree. Arterial thrombi and emboli have been discussed previously.²

THE LOCALIZATION OF THROMBI

The primary source of thrombi in the venous system is not always obvious. The clinical importance of the thromboses in the lower extremities and the pelvis is so great that one need simply mention the thromboses in the upper extremities as being comparatively infrequent and brought on either by trauma, as the axillary thrombosis of effort, or following axillary dissection, as a carcinomatous periphlebitis, or following intravenous injections or infusions. The majority of thrombi, however, form in the lower extremities and the pelvic veins. It is not sufficiently recognized that from 50 to 60 per cent of all adults carry thrombi in the plantar veins or veins of the calf muscles,³ that phleboliths are often seen in the x-ray films of the pelvis, and that the broad ligament frequently carries plugged veins transected during hysterectomies.⁴

We are grateful for the co-operation of Dr. N. C. Gilbert, Dr. G. K. Fenn, and Dr. G. W. Scupham of the Department of Medicine, Dr. E. L. Jenkinson of the Department of Roentgenology, and Dr. E. F. Hirsch of the Department of Laboratories, St. Luke's Hospital, Chicago.

Received for publication, Aug. 21, 1944.

It has been customary since the teachings of the older pathologists to regard *slowing of the circulation, changes in the vessel wall, and increased coagulability of the blood* as the three factors responsible for thrombosis.

Slowing of the Circulation.—This factor alone will hardly ever suffice to produce thrombosis. Blood may stay fluid between two ligatures if

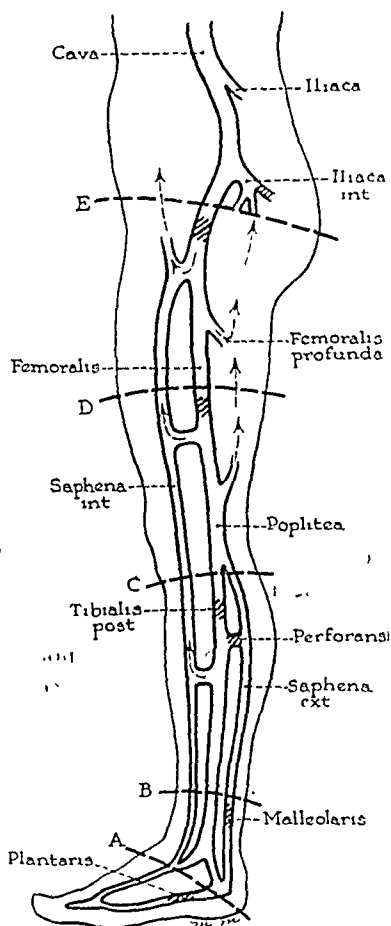


Fig. 1.—The primary sources of deep venous thrombosis in the lower extremity. Mechanical obstructions localize such thrombi to certain segments. A, Tendon of peroneus longus crossing plantar vein; B, upper margin of malleolar ligament; C, upper edge of soleus muscle; D, adductor canal; E, inguinal ligament.

care is taken not to injure the intima, but when other factors are present it will serve to localize the clot to a certain segment. The post-operative state and the prolonged bed rest of the cardiac with slow circulation times predispose to thrombosis; the constricting action of ligaments, tendinous insertions, and bony prominences may determine the segmental localization of the thrombi (Neumann³). (See Fig. 1.) Obviously, however, since such constrictor and compressing influences operate in all of us, they do not suffice alone to produce clotting.

Injury to the Intima.—Mechanical trauma, such as tearing, crushing, or stretching a vessel, operates in many cases of thrombosis following fractures, sprains, gunshot, and stab wounds. The vessel itself does not have to be directly injured. Many ankle sprains, fractures of the lower leg, knee, and pelvic injuries are seen daily which start a thrombus at the site of injury. Infections such as occur in bacterial endocarditis, typhoid fever, pneumonia, or scarlet fever may localize to the intima of a peripheral vessel, producing a raw surface and a deposition of platelets.* The vessels may also be sensitized to allergens, producing damage.⁵ Ulceration of an atheromatous plaque in the aorta produces thrombosis. Aneurysms invariably harbor thrombi.

Increased Coagulability of the Blood.—There are many states in which the blood clots more readily. Any trauma which liberates thrombokinase from the tissues will do so; this occurs after massive injuries to muscle and after any major operation. Loss of plasma in burns and shock, dehydration due to vomiting, or rapid diuresis after mercurials produces hemoconcentration and increased viscosity. Patients with polycythemia or those suffering from carcinoma also have a tendency to blood-clotting, possibly because of rapid destruction of platelets which liberate thrombokinase in the former, and because of tissue destruction in the latter.

PROPHYLAXIS OF THROMBOSIS

What are the measures one can employ to minimize the operation of these factors? In combating the retardation of blood flow, most surgeons are cognizant of the importance of early mobilization of patients. It can be statistically proved that prolonged immobilization of an identical group of patients will lead to a higher incidence of thrombi and emboli. But obviously many patients cannot be mobilized for eight to twelve weeks, for example, those suffering from severe abdominal infections or fractures at certain sites. Elevation of the foot of the bed on chairs or on shock blocks is an excellent, simple procedure to accelerate venous return from the lower extremities. The pelvis must be included in this reversed drainage (Figs. 2 and 3). Years ago we advocated a stationary bicycle attached to the patient's bed but this can be easily substituted by having the patients dorsiflex and plantarflex their ankles, which exercises their calf muscles and empties the veins. Naturally all these measures have their contraindications and limitations.

It is difficult to see how one could prevent trauma, whether mechanical, thermal, or bacterial, once it affects the vessel wall; but one can help to localize and prevent the mural thrombus from breaking loose by measures to be discussed presently.

The interest in preventing *excessive coagulability of the blood* has arisen since the advent of purified and comparatively nontoxic anticoagulants.⁶ In order to use such drugs preventively and not only

*Atypical (virus) pneumonia seems to predispose to clotting.

therapeutically, it became necessary to look around for a simple diagnostic test which would detect early changes in the clotting mechanism. The customarily employed tests of clotting time and bleeding time do not reveal any clear-cut changes. Prothrombin time determined on diluted plasma does detect a tendency toward increased clotting but the method requires skilled laboratory technique.⁷ The response of such patients

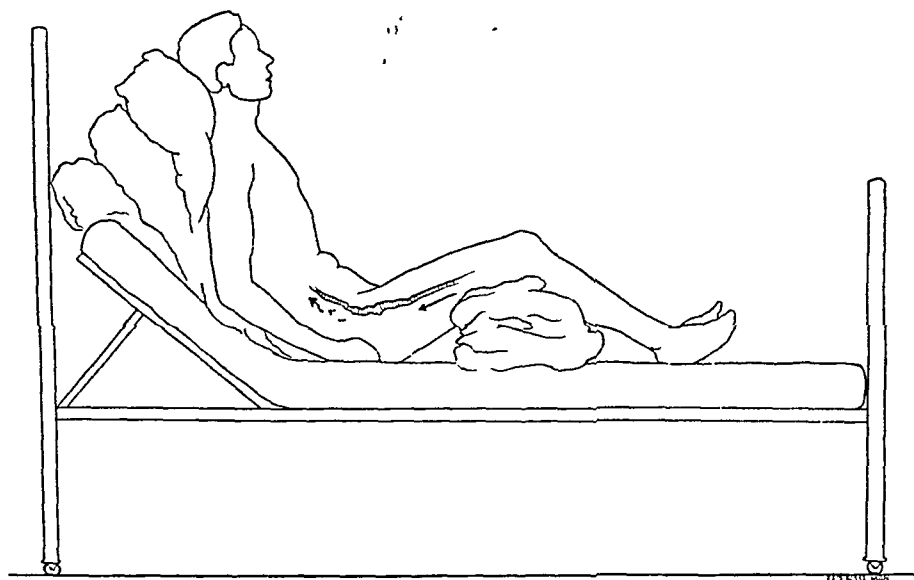


Fig. 2.—Pooling of blood in the popliteal fossa and in the pelvis during the customary Fowler's position. (From de Takats, G., and Jesser, J. H.: Pulmonary Embolism, J.A.M.A. 114: 1415, 1940.)

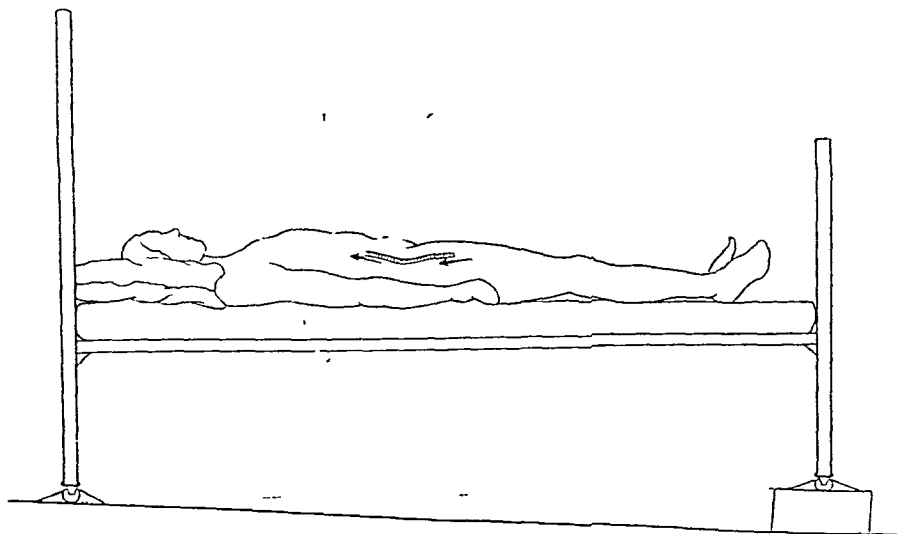


Fig. 3—Much better venous drainage is accomplished by the Trendelenburg position. The circulation time from foot to tongue is demonstrably accelerated. The foot of the bed is elevated and not the lower leg alone. (From de Takats, G., and Jesser, J. H.: Pulmonary Embolism, J.A.M.A. 114: 1415, 1940.)

to heparin is strikingly diminished and this decreased heparin tolerance has been used extensively for determining the increase in clotting factors. Such factors have been shown to exist in the postoperative state, in Buerger's disease, and in the presence of any kind of intravascular clotting.^{8a} Other factors such as neurogenic influences^{8b} and the thromboplastic properties of digitalis^{8c} have been investigated. Conversely, drugs like prostigmine^{8b} or sulfur compounds^{8d} seemed to decrease the increased clotting factors. It has been found practical to determine the heparin response of such patients, who were either suspected of harboring thrombi or who have shown previous evidence of thrombosis. One cubic centimeter (10 mg.) of heparin is injected intravenously. Coagulation times are determined with a capillary tube before ten, twenty, and thirty minutes after the injection of heparin. A flat tolerance curve indicates the presence or imminence of thrombosis (Fig. 4). The normal response can be restored by heparin, by dicoumarol, by sulfur compounds, or by prostigmine.⁸ Patients sensitized to heparin can be detected.^{8a}

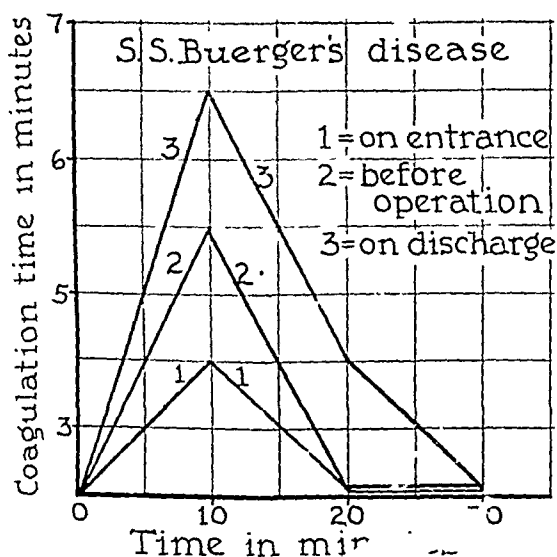


FIG. 4.—Three heparin-tolerance curves of the same patient, indicating a steady improvement of the clotting mechanism following treatment.

For the prophylaxis of postoperative thrombosis, the following drug therapy is used: In patients who have a pre-existing deep venous thrombosis, or have thrown arterial or pulmonary emboli from the heart, the heparin-dicoumarol combination is used when operations of any sort are necessary. In eighty-one such patients no extension of the clot and no emboli occurred. Three patients had major hemorrhages requiring transfusion. These occurred, however, in the first month of our experience. Three patients, all diabetics, presumably with hepatic damage, showed a marked response to a single dose of dicoumarol, necessitating intensive vitamin K therapy to bring the prothrombin level back to a moderately

subnormal level. Five additional patients had a hematoma at the site of the operation, mostly in the stump of an amputated leg. We shall discuss our present method of controlling the dosage of dicoumarol. It requires continuous watchfulness and should probably be carried out by the medical department, just as the dosage of insulin is regulated in the surgical diabetic. Sodium tetrathionate is used in the intravenous drip after sympathectomies for thromboangiitis obliterans. The dose is 0.6 Gm. to each 1,000 c.c. of salt solution. These patients do show an increased tendency to clotting. They also receive tetrathionate postoperatively until their clotting mechanism returns to normal (Fig. 5).

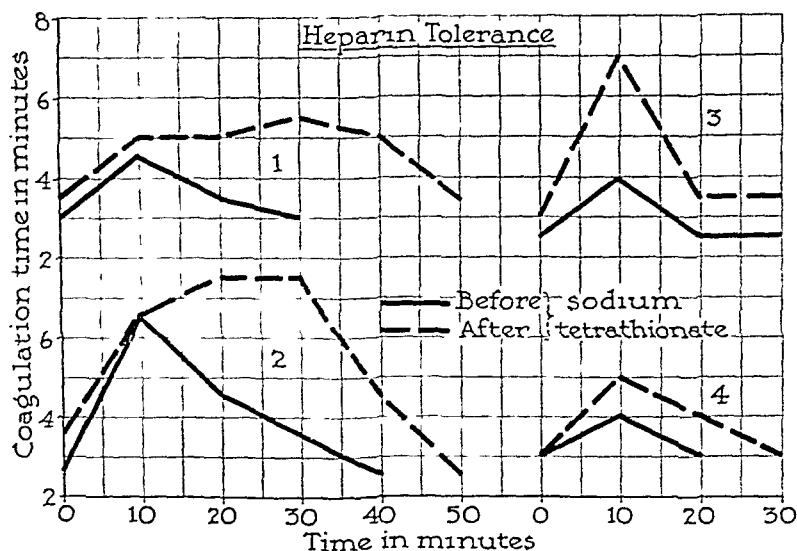


Fig. 5.—Heparin tolerances of four patients all of whom had intravascular clotting. Note that all four developed a better response to heparin. The least response is shown by the patient in Case 4, who had multiple emboli following coronary thrombosis, one of them resulting in gangrene of the left lower extremity. His response to sodium tetrathionate was very small, indicating a marked clotting tendency. (From SURGERY 14: 663, 1943.)

Prostigmine, which equally seems to improve the patient's response to heparin, is used after all laparotomies, especially pelvic. Its effect on postoperative intestinal and bladder atony has been noted many times. One cubic centimeter of 1:2000 solution is given every four hours, ten times. For some reason, which is not clear, it definitely affects the clotting mechanism.^{8b} The exact number of cases in which the prophylactic use of sodium tetrathionate and prostigmine was employed could not be ascertained. It has been employed since July, 1943, to date, on one active surgical and one active gynecologic service in several hundred cases. There was no thrombo-embolism in the group to which it was given.

THE CLINICAL SYNDROME OF VENOUS THROMBOSES

One need not describe the full-blown picture of iliofemoral thrombosis, with the inguinal pain, the massive edema, and the cyanotic hue

of the extremity. It is more important to realize that the iliofemoral segment is never the primary source of thrombosis but is the result of propagation from elsewhere. The following clinical pictures can be segregated from the several hundred cases which our group has studied.

Group 1.—Superficial phlebitis of pre-existing varicosities, ascending toward the groin. No, or very little, edema exists. No spasm in calf muscles is present. Large, red, painful thrombi are visible and palpable.

Migrating phlebitis in male smokers in the absence of varicosities, with no, or beginning, arterial involvement, makes one highly suspicious of Buerger's disease, which is not within the scope of this paper.

Attention should be directed to the not infrequently observed cases in which large superficial varicosities suddenly become thrombosed in the presence of an old deep venous obstruction. When these patients are treated by the usual combination of high ligation and injections the edema will not subside but may increase.

CASE 1.—Dr. A. E., a 72-year-old physician, had a slowly ascending thrombosis involving the entire long saphenous system, without fever and general systemic disturbance. He had varicosities since the age of 16, but had no discomfort except for the annoyance of having to wear elastic support. Only when the thrombus had obviously reached the groin did he consent to an operation.

Dec. 27, 1940, the left saphenous vein was exposed at the groin. There was a soft friable clot in the saphenous bulb which was aspirated and found to extend into the iliofemoral segment. With the use of an eyedropper attached to the suction apparatus, a large number of soft, friable, red thrombi were aspirated from the femoral vein. However, markedly adherent mural thrombi, obviously of earlier date, were also encountered.

Continuous intravenous drip was started with 600 mg. of heparin daily. Fluids were limited to 2,000 c.c.; coagulation time was kept around ten minutes (capillary coagulation time). A large hematoma developed in the wound, which was expressed through a small incision on the ninth day. At this time heparin was discontinued. The patient was discharged on the fourteenth day.

A re-examination six months later revealed a low-grade chronic edema. The veins were still tender and firm in the calf. A few doses of x-ray treatment helped to absorb the periphlebitic exudate. However, permanent elastic stocking is necessary. To date, four years later, he is in excellent health, has remarried, and still practices. Edema persists.

This was one of our first cases of aspiration and extraction. Today, we would be more inclined to ligate the femoral vein instead of aspirating it through the saphenous. Also, the use of continuous administration of heparin has been discontinued.

Note that the acute superficial phlebitis was superimposed on an old deep venous thrombosis. Such cases are comparatively frequent.

Group 2.—Pressure pain over the lateral aspect of the foot,⁹ later over the inner malleolus, then over the posterior tibial vein. There is pain or dorsiflexion of the foot.¹⁰ From day to day the clot seems to ascend; the thigh becomes tender and swollen. The femoral artery pulsates more feebly on the affected side but the calf and foot are warmer. The oscillations are increased over the affected side. Embolism is frequent when

the clot is below the knee, rare when typical milk leg is present (6.6 per cent).¹¹ Embolism often precedes the appearance of the femoral thrombosis. This is the syndrome of *ascending plantar vein thrombosis*. It occurs more frequently in young, ambulatory individuals.

CASE 2.—Mrs. E. V., a 26-year-old graduate nurse, suffered a fissure of the right patella without separation of the fragments, in an automobile accident. A circular cast was applied in a near-by hospital. The sole of the foot began to ache within twenty-four hours. The cast had to be removed in forty-eight hours because of severe pain in the inner malleolus. On arrival at St. Luke's Hospital, six days after the injury, there was slight edema of the right ankle and calf. The lateral aspect of the sole of the foot was tender on pressure. Dorsiflexion produced pain and defensive spasm in the calf muscles. The thigh was not swollen and not tender on pressure.

This patient was treated with anticoagulants only, by a combination of heparin and dicoumarol, for ten days. Her convalescence was uneventful. She wore an elastic hose for three months. No residual edema developed. *This patient could as equally have had a ligation of the superficial femoral vein below the profunda. Since she needed immobilization because of the fracture, only anticoagulant therapy was used. No emboli phenomena occurred in this series of cases.*

Group 3.—No plantar vein involvement is present, but there is ache, cramp, and tightness in calf muscles. There is spasm on dorsiflexion, and increased temperature over the affected calf, with increased oscillations. The femoral vein is not tender; temperature and white count are normal. Emboli are frequent. The process may ascend to the popliteal or femoral vein as in the first group, but it is less apt to produce emboli. This is the syndrome of *calf muscle thrombosis*.¹⁰ It occurs more often in the older, immobilized group, but is frequently latent and unrecognized until embolism occurs.

Group 4.—Pain and swelling in buttocks or in adductor muscles close to the inguinal fold occurs. Sciatic neuritis is present. Frequency of urination, mucous diarrhea, or slight suprapubic edema is observed. Palpable cords lateral to the prostate or to the uterus may confirm the diagnosis. An embolus is not infrequent as long as thrombosis is intrapelvic; it is not so likely after extension to the external girdle. This is the syndrome of *pelvic vein thrombosis*.

There are, of course, combinations and transitions from one group to another. Generally speaking, the more latent and bland the thrombus is, the greater its embolizing possibility. In fact, the thrombus is most frequently evident after one pulmonary infarct has taken place.

The role of infectious versus bland thrombi, as discussed by Aschoff,¹³ and Ochsner and De Bakey,¹⁴ is not always easy to evaluate. A traumatic or mildly infected thrombus might propagate as a bland, red, nonadherent clot, which breaks loose easily. A bland phlebothrombosis might develop into an inflammatory periphlebitis when it ascends to the inguinal lymphatics, which often harbor infection.

The amount of edema depends on the extent of blocked collaterals,¹⁵ on the extent of the periphlebitic lymphatic obstruction,¹⁶ and on vaso-

spasm.¹⁷ These factors need special attention when planning treatment. They may all be present in the same patient in varying proportions.

METHODS OF TREATMENT

1. *Conservative Treatment.*—For centuries, the swollen milk-leg was immobilized and elevated, the patient being kept in bed for an arbitrary four to six weeks. The edema may be mobilized by mercurial diuretics¹⁸ although our recent studies would indicate that sudden dehydration may lead to increased tendency to clotting, so that the use of diuretics has been abandoned (Table I). The patient must wear a stocking from toes to groin for six to twelve months. That many patients have done well under this management can be best illustrated by Case 3.

CASE 3.—H. J., a 30-year-old woman, developed a left-sided iliofemoral thrombosis at home the twelfth day after childbirth. While at the hospital she complained of cramping in the calf, which was disregarded. When seen at home in 1941, three weeks after delivery, there was a massive swelling of the entire lower extremity. She was told to stay in bed for ten days after the pulse had returned to normal and wear an elastic stocking for six months. Salyrgan was prescribed twice a week. At examination three years later, no trace of edema and no varicosities were found.

TABLE I

THE EFFECT OF RAPID DEHYDRATION ON HEPARIN TOLERANCE (A. W.)

DATE	CONTROL	COAGULATION TIME IN ¹ MINUTE			WEIGHT IN NDS	REMARKS
		10	20	30		
1/23	3½	5	3½	3½	19½	Digitalis, gr. 6, from 1/21 to 1/24
1/25	3½	6	3½	3½	188	Digitalis, gr. 1½, daily until 2/10
1/26	3½	6½	5	3½	186	Mercupurin, 1 c.c.
1/27	3½	4½	3½	3½	175	
1/28	3½	5	3½	3½	168	Lost 18 lb. of fluid in 2 days
1/29	3½	4½	3½	3½	166½	
1/30	3½	4½	3½	3½	166½	
2/ 1	3½	3½	3½	3½		Irrational
2/ 2	3½	3½	3½	3½		Mercupurin, 1 c.c.
2/ 3	3	3	3		156	Lost 11 lb. of fluid; irrational and incontinent
2/ 4	3	3	3		154	
2/ 6	3	3	3		148	
2/ 7	3	3	3		148	
2/ 8	3	3'45"	3		150	
2/ 9	3	3	3			
2/10	3	3	3		156	Digitalis stopped

Criticism of the Method: The difficulty is that the residual edema and the possibility of embolism are entirely left to chance. If the clot is not too extensive, the swelling will be negligible, especially if elastic support is worn for a long time. Immobilization is long and the loss of time is great. The danger of embolism, if the femoral segment is occluded, is small, but the process may involve the other extremity in approximately one-third of the cases.

2. *Anticoagulant Therapy.*—If one lays stress on the danger of the propagation of the clot and the lack of fixation of the most recently

formed red thrombus, the use of anticoagulants seems indicated. Heparin is given at four-hour intervals in 50 mg. doses undiluted, intravenously. While this will not maintain a steadily elevated coagulated time, it is simpler for the patient and its protective value is equally efficient. Simultaneously, oral administration of dicoumarol is started, 300 mg. the first, and 200 mg. the second, day. Prothrombin levels must be determined daily (Fig. 6). The level must be kept between 60 and 30 per cent of the normal prothrombin time and the dosage of dicoumarol

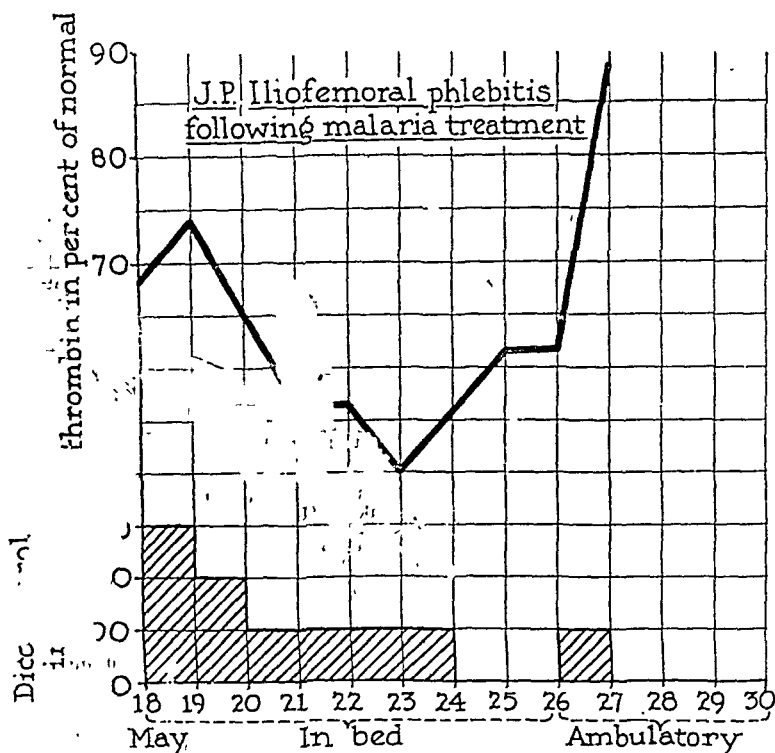


Fig. 6.—The routine treatment of iliofemoral thrombosis with anticoagulants. The administration of 5 c.c. of undiluted heparin given every four hours for the first two days is not shown in the graph. This patient arrived at the hospital two weeks after the completion of a course of fever therapy for general paresis. His history was typical of an ascending lower leg thrombosis. He received dicoumarol for six days and was made ambulatory on the eighth day, by which time the pain and edema had disappeared. One more dose of dicoumarol was given at the time when he was made ambulatory.

must be adapted to the daily determinations. Heparin is discontinued usually after two days, when the action of dicoumarol has become manifest. Dicoumarol is used until the patient is ambulatory, which may be as early as eight to ten days, unless an infarct or some other complication prevents it. In some patients with recurrent thromboses, in polycythemia with multiple thromboses, or in recurrent embolizations from the heart to the peripheral arteries, dicoumarol has been given for many months, with control of the prothrombin level once a week. When dicoumarol is suddenly stopped, a thrombosis may become manifest.

Criticism of the Method: Propagation of thrombosis or embolism has been said to have occurred during or immediately after discontinuation of the anticoagulant.¹⁹ With adequate dosage and slow tapering off with discontinuation of the drug, we have not observed such phenomena. More objectionable is the difficulty of control and the danger of hemorrhage in postoperative patients.

CASE 4.—A. G., a 56-year-old optometrist, had had fibrillations for many years. Two weeks before entrance to the hospital he suffered a cerebral embolus. Ten days later a right femoral embolus occurred which was not seen by us until three days later, when the lower leg was obviously lost. It was amputated just above the knee. Dicoumarol was promptly started with heparin. The prothrombin levels are shown in Fig. 7.

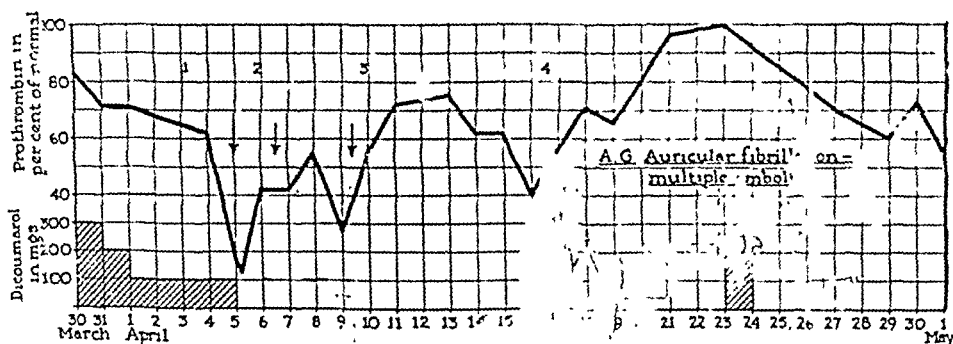


Fig. 7.—Prothrombin levels on A. G., a 56-year-old optometrist, with known fibrillations for many years, who entered St. Luke's Hospital March 29, 1944, because of a right femoral embolism suffered forty-eight hours previously. A week previous to this vascular accident he had a cerebral embolus producing considerable difficulty with speech. On examination the right lower extremity was obviously lost, but it was packed in ice with the hope of gaining some time for collateral circulation. Dicoumarol was started promptly with the customary schedule of 300, 200, and 100 mg. for the first three days. After six days of dicoumarol, the prothrombin level dropped to 17 per cent of normal and this was all the more underlined since a guillotine amputation of the right leg was performed under refrigeration on April 3. A huge hematoma formed in the stump. (1) Amputation; (2) 50 mg. of vitamin K given intravenously April 5 and 7 raised the prothrombin level to 53 per cent of normal, but next day it fell again to 28 per cent. Another 50 mg. of vitamin K and 500 c.c. of blood were given at (3). At (4) it was necessary to start digitalin, gr. 1½, three times a day intramuscularly. Dicoumarol had been stopped April 5, but a single dose of 200 mg. was given again, April 23. This patient was sensitive to dicoumarol, possibly because of a cardiac cirrhosis of the liver. The effect of vitamin K was temporary. The effect of digitalis may have raised the prothrombin level to a level never reached before. Owing to an error of the resident staff, and in spite of a standing order, he received no dicoumarol on April 18 and thereafter, when his prothrombin level began to rise. He died of multiple pulmonary emboli from the right heart. This graph indicates some of the difficulties encountered when dicoumarol is administered. Both vitamin K and digitalis may have increased the clotting tendency, whereas the hepatic damage made the patient sensitive to dicoumarol.

3. Paravertebral Sympathetic Block.—Some of the symptoms following venous thrombosis are due to a spasm in the peripheral vascular tree. This is especially evident when the iliofemoral segment is suddenly occluded and is surrounded by a periphlebitic exudate. A paravertebral block of the lumbar sympathetics will relieve the pain and much of the edema and restore the arterial pulsations, which are frequently diminished. They may even be absent and give rise to the diagnosis of arterial embolism.

A case in point is that of H. R.

CASE 5.—H. R., a 52-year-old man, entered St. Luke's Hospital Dec. 1, 1943, with an attack of nausea, vomiting, and abdominal distention.

Past History.—In July, 1942, the patient had a myocardial infarct, since which time occasional anginal pain occurred. He had been taking unknown amounts of digitalis off and on, on his own volition, until the time of entrance to the hospital.

Diagnosis of acute posterior infarct was made and emergency treatment instituted. He rapidly improved but twelve days after admission, after preliminary abdominal and left suprapubic cramping, the entire left lower extremity became cyanotic and pulseless. Pain was intense at the groin. Edema was marked only in the thigh. The adductor muscles were tender on pressure.

Diagnosis of left iliofemoral thrombosis was made with reflex arterial spasm. Papaverine, gr. 1, by mouth did not relieve the pain. Paravertebral block resulted in restoration of color and arterial pulses. The foot of the bed was elevated on a chair. Heparin-dicoumarol treatment was started. Within twenty-four hours the circumference at the ankle was reduced by one inch and at the thigh by four inches. There was no difference between the two lower extremities.

Course.—Two weeks later the swelling in the thigh recurred; a hard inguinal lymph gland became palpable. A firm cord was felt left of the prostate, which was large and tender. X-ray was given to this area. The attack subsided and he was discharged with a rubber stocking after fifty-one days in the hospital.

Follow-up.—Three months later there was considerable edema at the ankle. He did not worn the stocking consistently, but unquestionably the second, periphlebitic stocking at the groin for this permanent edema.

Criticism of the method.—The method can be readily acquired with a little practice and seen to be less. It will not protect the patient from an embolus,²⁰ nor can it protect him from residual edema if the extent of the thrombus is too great. Whether it would localize a plantar vein or calf muscle thrombosis by releasing venospasm proximal to the clot is not certain, but phlebograms have been reported demonstrating the release of venospasm following sympathetic block.²¹

Sympathetic block may be useful many years following an iliofemoral thrombosis. It is then capable of relieving a chronic causalgia-like pain with edema which originates in the periphlebitic reaction around the occluded vein. Stripping such a vein has been useful,²² but one or two sympathetic blocks may be equally effective.

The following case is illustrative.

CASE 6.—G. D. S., a 54-year-old lawyer, developed cramping in the left calf following a bicycle ride in 1940. The pain and swelling ascended to the groin and to the scrotum. When seen two years later there was a diffuse swelling from midcalf to groin. Following a paravertebral block with procaine and an adequate elastic stocking, the swelling of the thigh decreased 5½ inches. Six months later use of the stocking was discontinued. All pain and edema disappeared. In 1943 he developed a sudden pain in the gluteal region and along the sciatic nerve following the injection of a hemorrhoid done elsewhere. This subsided in two weeks and there was no recurrence of swelling during the last year.

4. *Proximal Vein Ligation.*—Many authors have advocated the extraction of the clot or the proximal ligation of the vein to prevent embolism.²³ The method seems obviously indicated when, after a pulmonary infarct, the site of thrombosis is recognized in one or both calves,

when the thigh is not swollen, and the femoral vein is not tender. Much less of an indication exists when the patient is seen in a stage of fully developed iliofemoral thrombosis, which is tender, adherent, and cannot always be completely extracted by suction. In such a situation the operation seems unnecessary unless one wishes to tie the common iliac vein, a procedure still under discussion.¹²

Criticism of the Method: Many femoral veins seem to be tied unnecessarily. The visualization of the deep veins of the lower leg has been advocated for a localization of the thrombus,²⁴ but in my experience it results in clear-cut information only when a clinical study is equally conclusive. Its results are questionable in many instances; the drug (35 per cent diodrast) may produce thrombosis in tortuous veins with retarded flow. The edema resulting from the ligature is negligible if the femoral vein is ligated below the profunda and if the profunda remains open. Some of our first experiences with ligation of the femoral vein indicated that thrombosis of the unobstructed collaterals may follow aspiration and produce massive edema. Ligation of the common femoral vein often leaves a huge edema.

CASE 7.—A man, W. B., entered St. Francis Hospital complaining of sudden cyanosis and dyspnea of thirty hours' duration. Prior to admission his left ankle swelled and the calf became painful.

Past History.—Two years previously the patient had a prostatectomy followed by dyspnea. There was an attack of pleurisy on the left side six months ago. He was a heavy drinker.

On admission the entire left leg was warmer than the right. It was not swollen in the thigh but the Homans sign was positive. A bedside film showed increased density throughout both lungs with multiple emboli. Aug. 9, 1940, the femoral vein was exposed at the groin. The vascular sheath was edematous. The artery was separated from the vein with difficulty. The vein was thick, edematous, and distended. The origin of the profunda was visualized and a braided silk ligature was placed just distal to it. A second ligature was placed one inch below the first one. The vein was cut and both ends were transected. Proximal to the ligature the vein was nicked; a glass suction tip aspirated a lot of small clots until bleeding was free from above. The incision was closed with interrupted sutures. The profunda was aspirated and free blood obtained. Heparin could not be administered since it caused a severe reaction in the patient.

Convalescence was uneventful. He was out of bed and walking about, but the left saphenous vein became red and tender. A definite phlebitis developed. This resulted in a residual edema, when the patient was seen one year later. Three years later there was a permanent moderate fibrosis and enlargement of the entire leg. He has to wear a stocking continuously.

CASE 8.—E. K., a woman 47 years old, had been under medical care for the past ten years for renal glycosuria, amenorrhea, repeated ankle strain, and five attacks of calf muscle thrombosis. There were several attacks of dizziness and choking with fever in her history. The perforating veins were incompetent below the knee. June 12, 1943, the femoral vein was exposed below the profunda. It was thickened, but empty, and was transected. Four months later, this leg was more cyanotic but not any more swollen than prior to the ligature. Eleven months later an acute phlebitis developed on the side of the femoral ligation. There were hard lumps in the previously incompetent perforators in the calf. Swelling and pain were considerable.

Elastic support and one week's course with 60 gr. of sulfadiazine helped to calm the process. While this patient was now protected from emboli, the attacks of phlebitis continued. Note also that the emboli occurred from a seemingly infectious, irritative type of clot.

*Roentgen-ray Therapy:** Since animal experiments convinced us that the absorption of thrombophlebitic edema may be hastened by x-ray therapy,²⁵ this form of treatment has been consistently used since 1933 in selected cases. While we have no knowledge of the effect of roentgen rays on the organization of the thrombus, the effect on the periphlebitic exudate and on the concomitant lymphangiitis and lymphadenitis is unmistakable. This effect is well demonstrable in cases of superficial periphlebitis and lymphangiitis, where one or two treatments visibly and palpably decrease the red, edematous streaks of inflammatory exudate. The dosage and the timing of repeated doses are important. If, in acute phlebitis, a dose of 200 r. units is given, a serious general reaction may occur with chills, fever, and a temporary bacteremia. Such a dose will be occasionally administered by an overzealous x-ray resident and is definitely inadvisable.

The surgeon should follow the results of roentgen therapy and not order another dose until the response to the first dose has subsided. One of us reported that a 30 to 40 per cent erythema dose of roentgen ray (125-135 r. units) with heavy filtration will produce a rise in temperature over the affected veins, which is markedly exaggerated compared with the response of a normal area.²⁶ If such doses are given repeatedly an exacerbation of phlebitis may result.

A surprisingly large number of patients have been seen who have gone through an active stage of deep venous thrombosis of the lower leg with or without embolization and with or without proximal ligation of the deep vein. A residual, latent infection may remain, with intermittent aching during changes in weather, slight local rises in skin temperature, and intermittent edema. A few small doses of roentgen-ray treatment are beneficial in this group, together with adequate elastic support. Case 9 is an example of this.

CASE 9.—Dr. H. D. had repeated attacks of pleurisy, until after the third one a deep thrombophlebitis in the left calf was discovered. He was treated by glycerin-gelatin casts. The thrombosis had reached the iliofemoral segment and was obviously of many months' duration. For four to five days at a time this leg would ache, swell more. There were persistently increased temperature and higher oscillographic readings over the affected limb. Three doses of roentgen-ray treatment consisting of 80 r. units with 2 mm. aluminum and $\frac{1}{4}$ mm. copper filter, given at one-week intervals, have effectively relieved the ache and some of the edema.

RESULTS OF TREATMENT

Conservative Therapy.—No figures are available since many hundreds of patients have been treated with conservative therapy. The residual

*The majority of these patients were treated by Dr. E. L. Jenkinson of St. Luke's Hospital. Thanks are also due to Dr. James B. Case, Dr. E. E. Barth, Dr. Gentz Perry, and Dr. Alfred C. Ledoux for their cooperation.

edema and the long period of disability, however, are marked, and an effort should be made for a more intensive type of therapy.

Anticoagulant Therapy.—All that can be said for the sixty-eight patients treated thus far is that not one of them developed an extension of the clot or an embolus, while they were receiving the drug.* Three patients had to have repeated courses of dicoumarol months apart since the original site of the clot became active again. One patient who had a femoral vein ligation and was kept on dicoumarol for ten days, when allowed to get up without further dicoumarol therapy, developed a thrombosis of the deep veins in the opposite leg. The superficial femoral vein was promptly tied on the second side. No edema developed. She was kept under dicoumarol for one month. Three patients are under continuous dicoumarol treatment, taking 300 mg. a week, but how long this can be kept up without any damage is not known. One of these has recurrent attacks of retinal vein thrombosis. Another, with rheumatic heart disease with multiple emboli to brain and extremities, controls her dosage with capillary coagulation times. The dosage has now been so regulated that she takes 300 mg. whenever the coagulation time returns to two minutes. A third patient takes 100 mg. five days of a week; this is far too much for the average patient, but her polycythemia makes her unusually resistant to dicoumarol.

Paravertebral Block.—We have used this paravertebral block occasionally since the report of Leriche, and more extensively since the reports of Ochsner and De Bakey.¹⁷ If the block is done early in the painful iliofemoral type (Group 3) it may hasten convalescence and disappearance of edema. However, with papaverine, heat to the abdomen, and high (eight to ten inch) elevation of the foot of the bed, our results are not much inferior to that obtained by paravertebral sympathetic block. We now limit the use of the method to patients whose arteries are in noticeable vessel spasm, whose toes are cold and blue, and who suffer great pain. Most patients, however, exhibit warm toes, large oscillations, and other evidence of inflammatory hyperemia. The results of paravertebral block in the late edemas, with neuritic pains aggravated by weather changes, are often striking. One or two injections combined with elastic support have relieved patients from long-drawn-out discomfort. Seventy-eight patients in a group have been injected for thrombophlebitis, but the method is used far less frequently than formerly.

Ligation of the Femoral Vein.—After trying this method in different types and different stages of thrombosis, the following indications have crystallized in our hands. (1) When the patient has had an infarct, wholly unexpected, the source of it is carefully investigated. If

*This statement requires modification since we have started the use of vitamin K to restore excessively low prothrombin levels. In two patients who showed unusual sensitivity to dicoumarol in that their prothrombin level quickly dropped to below 30 per cent of normal, the intravenous administration of vitamin K in 50 mg. doses resulted in a new vascular accident, which seemed to coincide with the administration of the vitamin. Further observations are obviously needed.

it is found to be in the calf muscles of the leg, the femoral vein is promptly tied below the profunda. (2) When the patient develops a recognizable calf muscle thrombus, which has been present for less than one week and the patient is immobilized for some other reason, the femoral vein is tied. Often a floating thrombus will be found in the common femoral vein.^{12, 20}

When, however, the patient is seen with a tender, swollen thigh or groin, the clot is not aspirated nor is the vein ligated above the profunda. Also, if the thrombus is below the knee but the patient has been ambulatory for more than one week without any extension to the thigh, the vein is not tied.

A total of thirty-nine femoral vein ligations have been done since 1940.* Some of these in the light of our present experience were entirely unnecessary. One of the greatest difficulties is the estimation of the age of the clot at the level of exposure. The clot is usually much older than one imagines. When it firmly adheres to the wall its aspiration from the proximal segment is difficult and leaves mural thrombi; furthermore, it has lost its embolizing property. When the clot is recent, friable, and nonadherent, its presence is not manifested by pain or edema in the thigh. We agree with Bauer²⁰ that these are the most dangerous clots and the ones that need ligation.

TABLE II
DIVISION OF THE FEMORAL VEIN
(1940 TO 1944)

SITE OF DIVISION	NUMBER OF CASES	RECURRENT PHLEBITIS	PERMANENT EDEMA
Superficial femoral	15	2	2
Common femoral	10		10

All patients received anticoagulants in the immediate postoperative period. There was no pulmonary embolism. All patients wore elastic hose to the groin on discharge

Ligation of the femoral vein above the profunda invariably results in considerable edema (Table II). We have not tried the ligation of the common iliac, but this should result in less circulatory embarrassment than when the common femoral is tied.¹² Nor has the vena cava been ligated in this series.†

The attitude of our group toward phlebograms has always been rather pessimistic. The information derived is often not in keeping with its hazards and inconveniences. We do use it if a topical diagnosis of venous occlusion is not possible. Circulation times from ankle to tongue are helpful.

*Twenty-five patients were re-examined from six months to three years after operation.

†Since this article was submitted for publication, the important contribution of Homans has appeared on the ligation of the common iliac vein or the vena cava for the bland ascending thrombosis. It is our feeling that the floating, nonobstructive clot at the iliofemoral segment is very reoperatively from an obstructive clot with well-established collateral circulation. Recently therapy has been our method of choice in such cases. Common iliac vein were done by Dr. J. T. Reynolds at St. Luke's

X-ray Treatment.—This type of treatment was given a trial in superficial phlebitis of varicose veins, in the iliofemoral thromboses with lymphadenopathy, in the migrating type of superficial phlebitis, and in the chronic latent deep phlebitis with exacerbations. The treatment is obviously directed against the periphlebitic infiltration and exudation. Naturally it will be least effective in the type of lesion which is activated by reinfection or allergic processes. In the migrating type of phlebitis seen in Buerger's disease, the response has not been satisfactory. The total number of cases on record is 74. Of these the diagnosis was varicose phlebitis in 35, migrating phlebitis in 10, iliofemoral thrombophlebitis in 26, and chronic latent phlebitis of the lower leg in 3 patients. Many of these cases would be treated today by a short intensive therapy with sulfanilamide. Penicillin in moderate doses, 15,000 units intramuscularly every four hours for five days, has given surprising results in three cases of migratory phlebitis; this type of treatment, however, has only been started and further experience is necessary to estimate its value.

PULMONARY EMBOLISM

Again there is no need to discuss in detail the classical picture of the massive pulmonary embolus, which obstructs the main artery or its two branches simultaneously and which kills the patient in less than ten minutes. But as pointed out previously, only 8.3 per cent of patients die in less than ten minutes, and 33 per cent die in less than one hour. Approximately 60 per cent of the patients with fatal emboli live from one hour to several days.²⁷ These figures only refer to the fatal emboli, but it is sufficiently known that only about one-fifth to one-fourth of these emboli are fatal at the first insult.¹¹

TABLE III
PULMONARY EMBOLISM

RECOGNITION
Sudden onset of shock with rapid weak pulse, restlessness, difficult, rapid breathing, sweating and pallor, pain in chest, fainting, collapse, or unconsciousness. Apt to be in a patient who has phlebitis, is convalescing from an operation or delivery, or is a known cardiac.
EMERGENCY TREATMENT
<i>By Nurse</i>
1. Place in semisitting position.
2. Start oxygen by catheter or mask immediately. Tanks are on each floor.
3. Give $\frac{1}{75}$ gr. atropine sulfate, hypodermically, immediately.
4. Call intern.
<i>By Intern</i>
1. Give a second dose of $\frac{1}{60}$ to $\frac{1}{75}$ gr. atropine sulfate intravenously (if previous injection of atropine has not caused flushing of face and dilation of pupil).
2. In any case give $\frac{1}{2}$ gr. papaverine hydrochloride intravenously.
3. Repeat atropine and papaverine three or four times a day.
4. Order portable chest film and electrocardiogram.
<i>Note</i>
Morphine, adrenalin, or digitalis may aggravate the condition.

This treatment is useful even if patient is suffering from some other condition such as coronary occlusion or a cerebral vascular accident.

These figures mean that there is sufficient time to treat the majority of these patients, first of all for the episode itself, and second for the prevention of a second or third infarct which might become increasingly dangerous. The recognition of the early signs and symptoms has been stressed to the nursing staff. A small set of instructions is posted on each floor, since it has been our experience that in large hospitals much important time is lost until the intern arrives (Table III).

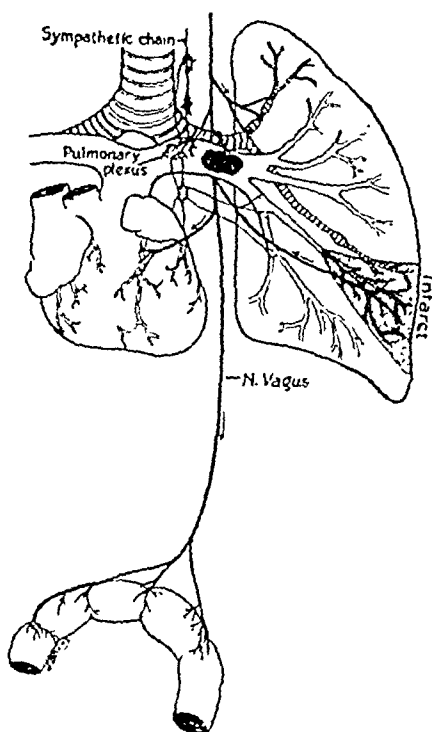


Fig. 8.—The radiation of autonomic reflexes in pulmonary embolism. The afferent impulses travel mainly in the vagus and radiate back to the lung as bronchoconstrictor and bronchosecretory fibers. They produce vagal inhibition of the heart and depress blood pressure. They can cause pylorospasm and intestinal colics, producing severe abdominal pain. (From *SURGERY* 6:239, 1939.)

The rationale of this emergency treatment is based on the assumption that embolism kills not only because of asphyxia, failure of the right heart, or insufficient venous return to the left heart. True enough, these conditions prevail when the main pulmonary artery or both right and left branches are simultaneously obstructed. However, we have shown post-mortem records to indicate that patients may die from a small embolus obstructing an insignificant area of the lung.²⁷ But also, on the basis of animal experiments, we have concluded that a widespread radiation of autonomic reflexes occurs during embolism, which affects the heart, the pulmonary vascular tree, the bronchi, and the gastrointestinal tract²⁶ (Fig. 8). These reflexes are predominantly vagal and produce spasm of smooth muscle; thus the use of atropine and papaverine seems indicated. Morphine and digitalis both sensitize the vagus and may thus facilitate such reflexes. Epinephrine, frequently employed in acute

hypotension, may lead to pulmonary edema in the presence of an increased pressure in the pulmonary artery which exists in cases of pulmonary embolism. These drugs have been tried in the animal experiment and have been shown to have deleterious action.

These emergency measures have been in use at St. Luke's Hospital for over four years. Of the forty-five patients on whom we have adequate records, thirty-five were relieved of their symptoms and did not die of that attack. Ten patients died with six autopsies. These autopsies showed massive arterial obstructions with coils of clots in the right ventricle; obviously this type of treatment could not help.



Fig. 9.—Pleural effusion following typical pulmonary embolism followed by ilio-femoral thrombosis. The embolus occurred ten days after cholecystectomy. The left foot and lower leg were slightly warmer. Repeated pleuritic effusions are not infrequently seen, being due to multiple emboli.

Attention should be called to the syndrome of the slowly fatal pulmonary embolism, when death finally occurs from right heart failure many hours or several days after the initial attack. If pulmonary embolism is to be done at all, in such a case a trial would be worth while, as Pilcher suggested.²⁹

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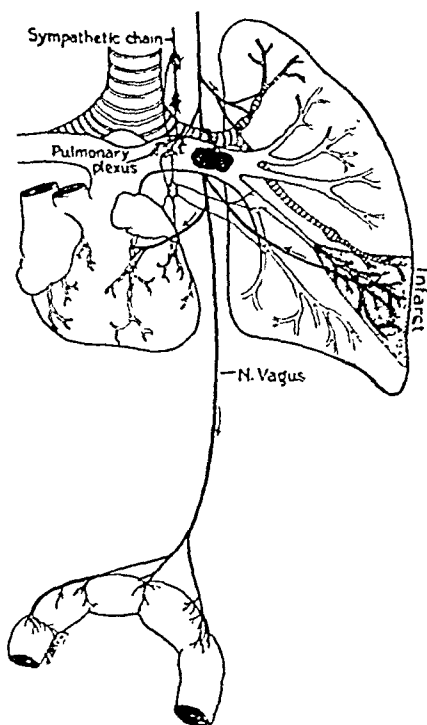


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Fig. 10.—Multiple pulmonary emboli following a punch prostatectomy, verified by autopsy. This patient was suspected of having multiple pulmonary metastases of carcinoma when he suddenly died from an embolus.



Fig. 11.—Atelectasis of the left lower lobe ten days after a hernia operation. In a previous communication²⁴ we stressed the mechanism of reflex pulmonary atelectasis following emboli or chest trauma.

that not all emboli produce hemorrhagic infarcts, anemic areas may be translucent areas of atelectasis or emphysema may be visible, depending on the extent of bronchial obstruction. Pulmonary effusions (Fig. 9), embolic atelectases (Fig. 10), and embolic pneumonias (Fig. 11) may so mask the origin of the lesion that the source of the embolus is not looked for. Following the survival of the first embolic episode the primary source ought to be eliminated if possible. In case of a thrombus in the plantar or calf muscle veins, the ligation of the superficial femoral vein seems indicated. We are unconvinced, as stated previously, that the ligation of the common femoral vein, in the presence of an iliofemoral thrombus is necessary. If the clot had been really loose it would not be there any more; if it is organizing, the operation is unnecessary; the clot may reform after a complete cleaning out and the iliofemoral segment in anticoagulant therapy is inadequate.

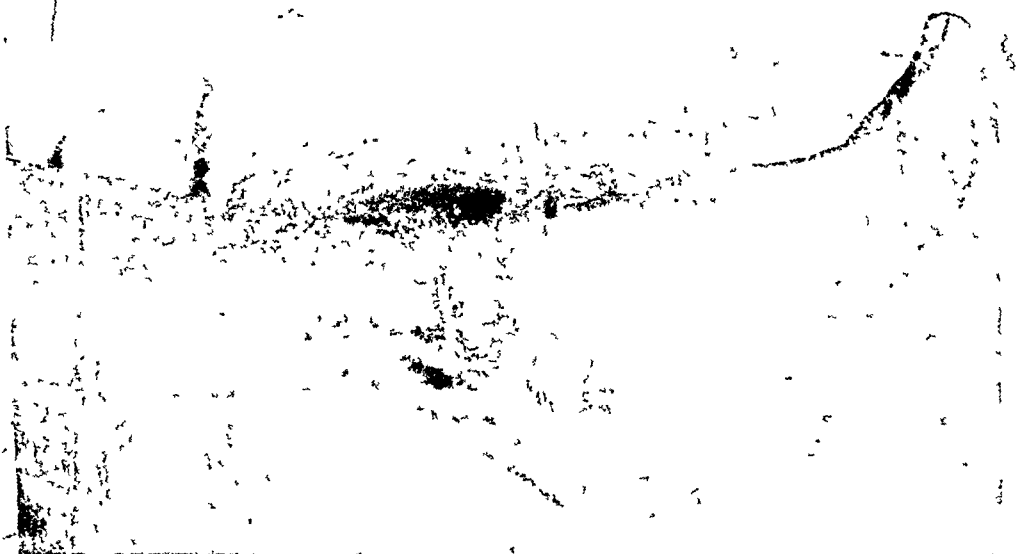


Fig. 12.—Dermatome graft on a chronic recurrent thrombophlebitic ulcer. Note small area of necrosis in the center of the graft, which came on two years after ligation. After two gelatin-glycerin casts the small defect readily healed.

If the primary source is in the pelvis or the right side of the heart, only anticoagulants can be of any use. These may increase hemoptysis or the pleural effusion but not to an alarming degree. In thirty-one patients receiving adequate heparin-dicoumarol therapy* in the presence of an infarcted lung, there has been no detectable increase in the size of the infarct.

On the contrary, we believe we have recognized, in conjunction with our medical consultant, Dr. G. K. Fenn, cases of pulmonary infarction

*By adequate therapy we mean the establishment of a prothrombin level between 30 and 60 per cent of normal which is jealously guarded from getting higher or lower.

- c. Idem: Surgical Treatment of Acute Vascular Occlusions, *S. Clin. North America* 22: 199-220, 1942.
- 3a. Rössle, R.: Ueber die Bedeutung und die Entstehung der Wadenvenenthrombose, *Virchows Arch. f. path. Anat.* 300: 180, 1937.
- b. Voegt, M.: Venenkrankheiten der Wadenmuskulatur bei Venenthrombose und langem Krankheitsverlauf, *Ibid.* 300: 190, 1937.
- c. Neumann, R.: Ursachen, Verlauf und Entwicklungsformen der Beinthrombose, *Ibid.* 301: 708, 1938.
- d. Hunter, W. C., Sneeden, V. D., Robertson, Th. D., and Snyder, G. A. C.: Thrombosis of the Deep Veins of the Leg, *Arch. Int. Med.* 68: 1, 1941.
4. Jones, H. O.: Personal communication.
5. Rich, A. E.: Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarthritis Nodosa, *Bull. Johns Hopkins Hosp.* 71: 315, 1942.
- 6a. Murray, G.: Heparin in Surgical Treatment of Blood Vessels, *Arch. Surg.* 40: 307, 1940.
- b. Crawford, C., and Jorpes, E.: Heparin as a Prophylactic Against Thrombosis, *J. A. M. A.* 116: 2331, 1941.
- c. Mayer, O. O., and Axelrod, V. H.: Studies on the Hemorrhagic Agent (4-Hydroxydicoumarin) II. The Method of Administration and Dosage, *Am. J. M. Sc.* 204: 11, 1942.
7. Brambel, C. E., and Loefer, F. F.: Significance of Variations of Prothrombin Activity of Diluted Plasma, *Proc. Soc. Exptl. Biol. & Med.* 53: 218, 1943.
- 8a. de Takats, G.: Heparin Tolerance. A Test of the Clotting Mechanism, *Surg. Gynec. & Obst.* 77: 31, 1943.
- b. Idem: The Nervous Regulation of the Clotting Mechanism, *Arch. Surg.* 48: 105, 1944.
- c. de Takats, G., Trump, R. A., and Gilbert, N. C.: The Effect of Digitalis on Blood Clotting, *J. A. M. A.* 125: 840, 1944.
- d. de Takats, G.: The Effect of Sulfur Compounds on Blood Clotting, *SURGERY* 14: 661, 1943.
9. Payr, E.: Gedenken und Beobachtungen über die Thrombo-embolic-Frage, *Zentralbl. f. Chir.* 37: 961, 1930.
10. Homans, J.: Thrombosis of the Deep Veins of the Lower Leg Causing Pulmonary Embolism, *New England J. Med.* 211: 993, 1939.
11. Barker, N. W., Nygaard, K. K., Walters, W., and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Embolism, *Proc. Staff Meet., Mayo Clin.* 16: 33, 1941.
- 12a. Homans, J.: Pulmonary Embolism Due to Quiet Venous Thrombosis Simulating Cardiac and Pulmonary Disease, *New England J. Med.* 229: 309, 1943.
- b. Idem: Deep Quiet Venous Thrombosis in the Lower Limb. Preferred Levels for Interruption of Veins; Iliac Section or Ligation, *Surg., Gynec. & Obst.* 79: 70, 1944.
13. Aschoff, L.: Lectures on Pathology, New York, 1924, Paul B. Hoeber, Inc.
- 14a. Ochsner, A., and De Bakey, M.: Thrombophlebitis and Phlebothrombosis, *South. Surgeon* 8: 269, 1939.
- b. Idem: Therapy of Thrombophlebitis and Phlebothrombosis, *Arch. Surg.* 40: 208, 1940.
- c. Therapeutic Considerations of Thrombophlebitis and Phlebothrombosis, *New England J. Med.* 225: 207, 1941.
15. Zimmermann, L. M., and de Takats, G.: The Mechanism of Thrombophlebitic Edema, *Arch. Surg.* 23: 937, 1931.
16. Homans, J.: Thrombophlebitis of the Lower Extremities, *Ann. Surg.* 87: 641, 1928.
- 17a. Leriche, R.: Recherches experimentales sur les oedemes chirurgicaux des membres d'origine phlebitique, *J. de chir.* 37: 481, 1931.
- b. Ochsner, A., and De Bakey, M.: Thrombophlebitis: The Role of Vasospasm in the Production of Clinical Manifestations, *J. A. M. A.* 114: 117, 1940.
18. de Takats, G.: The Management of Acute Thrombophlebitic Edema, *J. A. M. A.* 100: 34, 1933.
19. Wassermann, L. R., and Stats, D.: Clinical Observations on the Effect of 33' Methylene Bis (4 Dihydroxy) Dicoumarin, *Am. J. M. Sc.* 206: 466, 1943.
20. Bauer, G.: Venous Thrombosis, *Arch. Surg.* 43: 462, 1943.
21. Papper, E. M., and Imber, A. E.: The Use of Phlebography and Lumbar Sympathetic Block in the Diagnosis of Venospasm in the Lower Extremities, *SURGERY* 15: 402, 1944.
22. de Takats, G.: Reflex Dystrophy of the Extremities, *Arch. Surg.* 34: 939, 1937.

23. Allen, A. W., Linten, R. R., and Donaldson, G. A.: Thrombosis and Embolism; Review of 202 Patients Treated by Femoral Vein Interruption, *Ann. Surg.* 118: 728, 1913.
- 24a. Bauer, G.: A Venographic Study of Thrombo-embolic Problems, *Acta chir. Scandinav. (Suppl. 6)* 184: 1, 1911.
- b. Welch, L. M., and Faxon, M. M.: Thrombophlebitis and Pulmonary Embolism, *J. A. M. A.* 117: 1502, 1911.
- c. Starr, A., Frank, H. A., and Fine, J.: The Venographic Diagnosis of Thrombophlebitis of the Lower Extremities, *J. A. M. A.* 118: 1192, 1912.
25. Zimmermann, L. M., Gault, J. T., Halpern, S. S., and de Takats, G.: The Effect of Salyrgan and X-ray on the Rate of Disappearance of Thrombophlebitic Edema, *J. Lab. & Clin. Med.* 19: 243, 1933.
26. de Takats, G.: "Resting Infection" in Varicose Veins, *Am. J. M. Sc.* 194: 57, 1932.
27. de Takats, G., and Jesser, J. H.: Pulmonary Embolism; Suggestions for Its Diagnosis, Prevention, and Management, *J. A. M. A.* 114: 1415, 1910.
- 28a. de Takats, G., Beck, W. M. C., and Fenn, K. G.: Pulmonary Embolism, *SURGERY* 6: 339, 1939.
- b. de Takats, G., and Jesser, J. H.: Visualization of the Pulmonary Artery During Its Embolic Obstruction, *Arch. Surg.* 42: 1039, 1941.
- c. Jesser, J. H., and de Takats, G.: The Principal Factor in Pulmonary Embolism, *SURGERY* 12: 544, 1942.
- d. de Takats, G., Fenn, G. K., and Jenkinson, E. L.: Reflex Pulmonary Atelectasis, *J. A. M. A.* 120: 686, 1942.
- e. Middleton, W. S.: Abdominal Pain in Pulmonary Thrombosis, *Ann. Int. Med.* 18: 345, 1943.
29. Pilcher, R. S.: Slowly Fatal Pulmonary Embolism, *Lancet* 2: 942, 1938.
30. Hampton, A. O., and Castleman, B.: Correlation of Post Mortem Chest Tele-roentgenograms With Autopsy Findings, *Am. J. Roentgenol.* 43: 305, 1940.
31. Belt, Th. H.: Late Sequelae of Pulmonary Embolism, *Lancet* 2: 730, 1939.

ETIOLOGY AND PREVENTION OF THROMBOSIS OF THE DEEP LEG VEINS

A STUDY OF 400 CASES

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THE problem of venous thrombosis and its most serious complication, pulmonary embolism, rightly commands the continued interest of all physicians.

Although incorporated in the wealth of publications of past years, certain fundamental and now well-authenticated facts concerning venous thrombosis and embolism are much in need of reiteration and emphasis. Textbooks in all of the specialties of medicine have almost universally chosen to repeat shopworn phrases, many of which are no longer in keeping with newer and well-documented information. For example, all venous thrombosis is still commonly referred to as "thrombophlebitis." Yet, as Ochsner and DeBakey¹ have pointed out, the rational consideration of the mechanism and prognosis of venous intravascular clotting demands that it be divided into two types: (1) phlebothrombosis, defined as venous occlusion unassociated with inflammation, the clot being loosely attached to the vein wall and (2) thrombophlebitis, clotting associated with and dependent upon inflammation of the vein wall, with the result that such clots are usually firmly attached. We fully agree that such a distinction is basic and fundamental. There is, moreover, a woeful lack of appreciation as to which veins serve as the commonest sources of thrombotic emboli—a vital feature of the problem from the point of view of prevention and treatment. It is still generally assumed that pulmonary emboli usually arise from clots in the femoral or the pelvic veins or from the right side of the heart, disregarding the now ample data to the contrary. Still another long and fondly held fallacy is that only the surgical patient is in danger of sustaining a pulmonary embolus. Again published figures are disregarded, for it is a fact that patients suffering from medical diseases are fully as susceptible and just as frequently die from pulmonary embolism. Finally, there has been great neglect of the adage that "an ounce of prevention is worth a pound of cure" with respect to phlebothrombosis and pulmonary embolism. The literature has been, and still is, cluttered by papers dealing with methods of diagnosis, refinements and

modifications of these procedures, and suggested means of treatment, all assuming that willy-nilly, thrombosis will take place and that "closing the barn door after the horse is out" is the desirable thing. It is true that some writers mention possible means of preventing thrombosis but unfortunately they propose methods not easily carried out, or bury the paragraph on prevention so deeply and inconspicuously in a maze of discussion that the casual or inexperienced reader fails to grasp its significance.

After several years of experience it has become our conviction that the only real hope of lessening the toll of deaths from pulmonary embolism lies in the widespread acceptance of the newer and well-proved facts as to the causes, the nature, and the anatomic location of most instances of venous thrombosis. Progress cannot and will not be made until this is accomplished.

REVIEW OF PERTINENT LITERATURE

Lack of recognition that the deep veins of the leg are the most frequent site of thrombosis and the most prolific source of both fatal and nonfatal pulmonary embolism long remained unknown for two reasons: (1) symptoms referable to such thromboses are likely to be absent or so slight that they are overlooked clinically and (2) restrictions necessary for autopsy dissection of the extremities.

Frykholm³ credit Denckhoff² 1929, and Olow,⁴ 1930, with proving that the earliest clinical symptoms of thrombosis of the lower extremities appear in the sole of the foot and in the calf, suggesting that these are the initial seats of clot formation. As early as 1934, Romans⁵ in this country, supported by clinical and pathologic-anatomic observations, emphasized the great importance of the veins of the calf as areas of origin of ascending thrombi.

Very possibly because of lesser restrictions on the extent of dissections, the first extensive examinations of leg veins were done in Germany. Thus, Rössle⁶ in 1937 published observations based on 324 post-mortems in persons over 20 years of age. Of these, 88 (27.1 per cent) harbored thrombi in the veins of the calf. Concomitant thrombosis of the femoral vein was found 38 times. In only 7 instances did Rössle find thrombosis of the femoral or hypogastric veins in the absence of thrombosed leg veins. It was his opinion that although emboli originating from the leg veins are rarely fatal, they are nevertheless significant because it is from thrombi here, propagating into the femoral veins, that massive emboli spring. Even so, in carefully dissected preparations he discovered 3 instances of pulmonary embolism accountable for only on the basis of an origin from the calf veins.

Equally interesting is Neumann's⁷ report on a series of 165 consecutive autopsies in which the venous system was widely and thoroughly searched for thrombi, with particular attention to the veins of the lower

extremities. In the 100 subjects exhibiting thrombosis of the legs, the localization was: plantar region, 71 per cent; internal malleolar region, 17 per cent; leg, 87 per cent; thigh, 22 per cent. The calf veins were much more often affected alone (29 per cent) than were the plantar veins alone (12 per cent). Neumann postulated two clinical types of thrombosis, based on the site of origin: (1) a benign variety, starting in the veins of the legs and characterized by slow progression of the clots, increasing in frequency with age and having a tendency toward multiple but nonfatal emboli; and (2) a malignant form, centered in the plantar region and typified by rapidly progressing thrombosis, occurring in younger people, not rising in frequency with age and tending toward fulminating, fatal embolism of the lungs. He expressed the belief that the source for both types is a thrombus that has progressed into the veins of the thigh. Of his subjects with thrombosis of the lower extremities, 11.8 per cent had fulminating fatal pulmonary embolism, and of these more than 80 per cent had clots in the veins of the feet and calves. If one includes the cases of nonfatal multiple emboli, the lower extremities account for 52.8 per cent of the clots lodging in the lungs.

Putzer⁸ investigated 370 bodies for thrombi in the lower leg and observed calf vein involvement in 100 of these (27 per cent). The right side was affected slightly more often than the left, but in nearly all instances the process was bilateral. There were 47 men and 53 women, 86 per cent of whom were between 40 and 80 years of age. All but three were classified as medical rather than surgical.

A very thorough study of thrombosis of the pelvic and leg veins was published by Frykholm² in 1940. The following list gives the locations and number of instances in which he found clots: iliac, 2; hypogastric, 3; visceral pelvic, 5; femoral (above profunda), 4; deep femoral, 9; adductor muscle, 16; femoral (below profunda), 5; popliteal, 23; calf muscle, 39; anterior tibial, 0; posterior tibial and peroneal, 25; malleolar and plantar, 2. With negative results he also searched the veins of the gluteal region and the extensor musculature of the thigh. There were 24 examples of pulmonary embolism but Frykholm fails to state which of the many sources he believed to be responsible for the embolus. Always, he observed, progression of the thrombotic process was in the direction of normal venous flow.

Two of us (W. C. H. and V. D. S.), with the collaboration of Robertson and Snyder,⁹ routinely removed the calf muscles in an unselected group of 351 autopsies. Later we had the opportunity of testing the validity of our conviction that the most important etiologic factor in phlebothrombosis of the lower extremities is simply confinement to bed for any reason whatsoever for more than a brief period. In order to obtain adequate control clinically, this study was limited to one hospital (Multnomah County) and was continued until the total number of again unselected autopsies reached 200, the same number investigated

the first time.⁹ Our second study was extended to include dissection of the femoral veins and those of the adductor muscles, shown by Frykholm² to be almost as frequently occluded as the major veins. We are now in a position to compare results with previous investigators, save for the plantar veins.

On the basis of the findings in the 351 cases, published in 1941,⁹ we came to the following conclusions:

1. Thrombosis of the deep veins of the leg is appallingly frequent among middle-aged and older persons forced to bed for varying periods of time, the incidence of thrombosis being 52.7 per cent.

2. Bilateral involvement was found 110 times and unilateral, 75 times. The right side alone was affected a little more often than was the left. Thrombi formed in the veins accompanying the larger arteries far more frequently than in other veins and were present in the soleus muscle more often than in the gastrocnemius.

3. Fatal pulmonary embolism was responsible for 3.13 per cent of all deaths; in 45.4 per cent of the cases of death from such embolism the most probable source was thrombosed leg veins. There is good authority for the belief that although fulminating emboli often spring from the femoral vessels, thrombosis here represents an extension from older clots in the legs and feet. From the standpoint of prophylaxis and treatment, recognition of this is most important.

4. Lesser emboli frequently originate from the veins of the calf. Showers of these, even though of small diameter, may consist of long clots, which, by buckling or coiling, are capable of occluding even the major pulmonary arteries. Repeated embolic episodes are more frequent than a single massive attack. Multiple small fragments can also do harm, by placing an added burden on an already embarrassed circulatory system.

5. In this series there was little difference in the incidence of thrombosis between medical (53.2 per cent) and surgical (46.9 per cent) patients or between men (52.2 per cent) and women (53.5 per cent).

6. Phlebitis, either as a cause or as a complication of thrombosis, had a minor role in our cases (8.1 per cent).

7. As a rule, phlebothrombosis of the deep veins of the leg is clinically silent and for this reason is likely to be forgotten until embolic phenomena appear.

8. We are of the opinion that the greatest single factor favoring thrombus formation in the lower extremity is sudden confinement to bed of a previously ambulatory older person without the benefit of exercise or the aid of gravity in the maintenance of an efficient venous circulation.

9. Planned and supervised voluntary movement and the elimination of too much comfort for the legs should do much to reduce the incidence of thrombosis and its all too frequent sequel, pulmonary embolism.

PRESENT STUDY

As previously stated, our purposes were: (1) to compare two series of equal size from the same hospital, (2) to determine the incidence of thrombosis of the femoral and adductor veins, and (3) to learn, if possible, the effects of exercise on thrombus formation.

At the outset it was recognized that the number of individuals who could safely be exercised might be limited. Previous experience⁹ had shown that on occasion phlebothrombosis may occur within two days after beginning recumbency. For this reason, in order to be perfectly safe, all persons not known to have been ambulatory as recently as forty-eight hours before admission were excluded. Then, too, as is common in charity institutions, many suffered from senility, debility, serious cardiac disease, and other states, so that they could not or would not move voluntarily, and this, along with a shortage of nurses, made it impractical to attempt to institute passive movement or massage. So that our efforts would not be too disseminated, it was decided to concentrate on one department, medicine, leaving to individual wishes and initiative whether exercise would be ordered in other departments. Thus, the number of suitable subjects was certain to be small.

Listed here are the post-mortem findings in the 169 instances that proved suitable for comparison of the possible effects of exercise, or the lack of it.

Group I

In hospital forty-eight hours or over (exercised, or ambulatory up to forty-eight hours before death)

Without leg vein thrombosis		
Medical service	27	
Surgical service	5	32
	—	—
With thrombosis of leg veins		
Medical service	5	
Surgical service	2	7
	—	—
Total		39
Per cent exhibiting thrombosis		17.9

Group II

In hospital forty eight or more hours (not exercised) and nonambulatory before death

Without leg vein thrombosis .		
Medical service	46	
Surgical service	15	61
	—	—
With thrombosis of leg veins		
Medical service	42	
Surgical service	27	69
	—	—
Total		130
Per cent of nonexercised, nonambulatory patients with thrombosis		53.07

Exact comparison is, of course, impossible owing to the inequality of numbers in the two groups. Unfortunately too, the number of exercised persons is small, but, in so far as it is permissible to make any statements, the incidence of phlebothrombosis is 35.17 per cent less among those who were exercised.

All pertinent figures and percentages gleaned from the two studies have been listed in parallel columns in Table I.

TABLE I

COMPARATIVE DATA OF CERTAIN VASCULAR PATHOLOGY, SEX, AGE, AND SERVICE CLASSIFICATION OF TWO SERIES OF 200 AUTOPSIES EACH, PERFORMED AT MULTNOMAH COUNTY HOSPITAL

	FIRST	SECOND
Number of necropsies in series	200	200
Number having leg or thigh vein thrombosis	118	88
Per cent with phlebothrombosis	59	44
Number of instances with thrombosis of thigh veins	Not exam.	31
Per cent occurrence of thigh vein thrombosis	Not exam.	15.5
Number of patients with thrombi only in thigh veins*	Not exam.	3
Number of patients with combined leg and thigh vein thrombosis	Not exam.	28
Per cent occurrence of combined thrombosis	Not exam.	89.1
Fatal pulmonary embolism	7	11
Origin from veins of legs alone	4	9
From other than veins of lower extremities	3	2
Per cent of deaths from pulmonary embolism (200 cases)	3.5	5.5
Per cent of deaths from pulmonary embolism (phlebothrombosis series)	5.09	12.5
Instances of nonfatal pulmonary embolism	24	28
Total number of patients with pulmonary emboli (fatal and nonfatal)	31	39
Per cent incidence of pulmonary embolism (fatal and nonfatal)	15.5	19.5
Per cent of nonfatal pulmonary emboli (phlebothrombosis group)	20.3	31.8
Sites of origin of nonfatal pulmonary emboli:		
Leg veins alone		10
Either leg veins or elsewhere		9
Probably from other than leg veins		2
Positively not from leg veins		7
Percentage of phlebitis observed histologically	5.9	2.5
Sex classification (entire group)		
Men	131	136
Women	69	64
Age grouping (whole series)		
Youngest	16	15
Oldest	94	91
Average age	60.8	62.8
Service classification (total cases)		
Surgical	29	58
Medical	159	135
Mixed (two or more services)	12	7
Surgical patients with phlebothrombosis	16	34
Percentage	55.2	58.6
Medical cases with phlebothrombosis	95	51
Percentage	59.7	37.7
Mixed group with phlebothrombosis	7	3
Percentage	58.3	42.6

*One occurred in a patient three times hospitalized and in whom the femoral thrombus was fully canalized. The other two were located in the veins of the adductor muscle, not in the femoral vein.

It seems possible that the over-all reduction in the number of instances of leg vein thrombosis, from 59 per cent to 44 per cent (15 per cent), when carried out by the same workers, under like conditions and with identical criteria for the diagnosis of thrombosis, is ascribable to the prophylactic measures instituted at the start of the second series. In the first group 59.7 per cent of the medical patients had phlebothrombosis of the calf, while in the second study it was 37.7 per cent, a drop of 20 per cent. By way of comparison, 55.2 per cent of the surgical patients the first time showed leg vein thrombi, increasing to 58.6 per cent in the later group. In fairness it must be said that the total number of surgical cases was exactly twice that of the first study.

Death from pulmonary embolism in the new series totals 11, or an increase of 4. Taking these figures alone and without explanation, it would appear that the preventive measures failed to accomplish the desired end. Of the 11, there were 5 from the medical service and the rest from the surgical division. All, irrespective of service classification, suffered from conditions which themselves precluded exercises, or had entered the hospital after previously having been in bed too long to make it safe to move their legs. All of the medical patients suffered from congestive heart failure. Pulmonary embolism could have been prevented in these people only by prophylactic femoral vein ligation.

Of interest and of practical importance is that thrombosis of the thigh veins, particularly the femoral, seldom occurs except in conjunction with involvement of the deep calf veins. In our material there was one instance of fully healed thrombosis of a femoral vein in a man who had been hospitalized on three previous occasions, and two examples of thrombosis of small veins in the adductor muscles, neither of which extended into the femoral vein. Our observations are in keeping with those of Frykholm,² Rössle,⁶ Neumann,⁷ and Putzer.⁸

Once more we have demonstrated to our satisfaction that both fatal and nonfatal pulmonary emboli more often originate from clots in the calf veins or propagations therefrom than from any other veins. Nine of the 11 fatal embolisms arose from the legs. Ten of the 28 nonfatal emboli certainly came from the legs and 9 others may have, although other sources were possible.

Phlebitis, which we accept as an entity only in the presence of acceptable histologic evidence of inflammation, was even less frequent (2.5 per cent) than before (5.9 per cent), and we find it more difficult than ever to believe that it has anything much to do with causing or influencing the outcome of deep leg vein thrombosis.

The location of the thrombi according to muscles, or to unilateral or bilateral involvement, has not been charted because the differences between the two series are trivial. As in the first study, we can say that when thrombosis occurs in the legs it is likely to be bilateral and that clots will be found in and along the soleus muscle much more frequently than in the gastrocnemius.

Table II indicates the locations of venous thrombi in situations other than the lower extremity.

TABLE II

LIST OF VENOUS THROMBI FOUND EITHER ALONE OR IN CONJUNCTION WITH THROMBI IN THE DEEP LEG VEINS

Pelvic (broad ligament, periprostatic, periurethral)	42
Pelvic veins and/or right heart chambers	6
Right atrial appendage	2
Right ventricle	2
Renal vein	1
Hemorrhoidal veins	1
Total	54
Number of patients with both leg and other veins thrombosed	33
Number of patients without leg vein thrombosis but clots elsewhere	21
Per cent with pulmonary emboli (7 cases)	33

The extremes of age, as well as the average age of the two groups, are not significantly changed. The average age for the first group is 60.8 years and for the second, 62.8 years.

CLINICAL DIAGNOSIS OF PHLEBOTHIROMBOSIS

Always there will be patients who have been in bed for more than two days before calling a physician; others will suffer from illness or trauma that make prophylactic measures impossible or inadvisable, just as in our 11 cases of fatal pulmonary embolism. It is these groups to which diagnostic and therapeutic measures should be directed. They, and any adult who must go to bed, are in real danger of phlebothrombosis and pulmonary embolism. The literature is replete with papers concerned with the signs and symptoms, the diagnostic methods, and the means of treatment of phlebothrombosis, and the interested reader will have no difficulty in finding them. It is not within the scope of this paper to discuss these features. Rather, we wish to set forth proof of the frequent occurrence of deep leg vein thrombosis, to emphasize that here is the commonest of all sources for pulmonary emboli, and to reiterate our belief that while there is a place for diagnosis and treatment of phlebothrombosis, prevention is what should ever be uppermost in the mind of the attending physician.

PREVENTION OF VENOUS THROMBOSIS

Efficient return of blood from the deep veins of the extremities is dependent upon five factors, namely: (1) the circulation time, directly related to the effectiveness of the heart, (2) the compressive action of muscular contraction on veins, (3) absence or elimination of mechanical obstruction, (4) maintenance of normal negative pressure within the abdomen and thorax, and (5) gravity. The first of these needs no discussion.

The relation of circulation time to exercise has been well shown by Smith and Allen.¹ In a study of 86 persons it soon became apparent

that the most important influence on the time of blood circulation was the temperature of the skin of the extremities. The speed of flow was decreased when the skin here was cool, and accentuated when it was warm, irrespective of whether vasodilatation was reflexly produced by heat, direct application of heat, ingestion of alcohol, or sympathectomy. Two minutes of rapid active movement of a leg lying in the supine position invariably increased the speed of blood flow; elevation to a 30 degree angle of the extremities of supine subjects always increased circulation time, as did sympathectomy.

Following a study of about 500 patients given postoperative exercises and among whom, incidentally, there were no instances of venous thrombosis or pulmonary embolism, Potts and Smith¹¹ sought to substantiate their belief that simultaneous deep breaths and active leg exercises at regular intervals would vary the blood flow, not only in the legs, but also the pelvic venous cistern, and thus prevent stasis and thrombosis. Variations in the volume flow of blood in the inferior vena cava measured with a venturimeter, employing the Venturi principle of producing partial constriction of a stiff rubber tube connected with the cut ends of the inferior vena cava, were studied in 6 dogs. The results were identical in all. Simultaneous elevation of both hind legs produced an increase varying from 100 to 150 per cent in the volume flow of blood in the inferior vena cava. In lightly anesthetized animals, contraction of the muscles of the hind legs occurring coincident with their elevation produced an increase of more than 250 per cent in volume flow, abrupt in onset and returning to normal in 10 to 15 seconds. Accuracy of the observations was checked by isolation and ligation of both femoral veins, whereupon elevation of the legs produced practically no change in blood flow; release of the clamps was followed by a prompt rise. Normal respiration had little demonstrable effect on blood flow; deep respiration, produced by carbon dioxide, caused irregular changes. To test the validity of the observation of Luckhardt, Alpert, and Smith¹² that the reflex inhibition of respiration will temporarily obstruct the return flow of blood to the heart, Potts and Smith¹¹ simulated this condition by overinflating the dog's lungs. Blood flow from the inferior vena cava dropped to almost zero, but when the obstruction in the pulmonary bed was released, there followed a prompt and marked rise in blood flow. Simultaneous elevation of the hind legs, with deflation of the lungs, resulted in an enormous increase in blood flow.

Thus is afforded experimental evidence of the efficacy of exercise, of gravity, and of obstruction upon normal venous return.

An interesting medical sidelight of the bombing of London in 1940 has a bearing upon the factor of mechanical obstruction to the veins of the lower extremities. In a short paper, Simpson¹³ comments on the striking increase in the number of deaths from pulmonary embolism among elderly people who were solicitously cared for night after night in the shelters by allowing them to sit in a deck, or similar type, chair.

The wooden crossbar of these chairs caused pressure on the back of the thigh or on the popliteal vessels and the legs were dependent. Comparing the deaths from other common cardiovascular accidents such as coronary thrombosis and cerebral hemorrhage, in which there was no significant increase over the previous year, it developed that 24 persons had died from pulmonary embolism in 1940, in contrast to 4 in 1939. Many of these people first consulted their physician on account of swollen legs and the condition became known as "shelter leg."

None of the five factors mentioned in the first paragraph of this section can be overlooked or neglected if phlebothrombosis is to be prevented. It is shortsighted to treat a weakened heart and at the same time allow fluid to accumulate in the pleural or peritoneal cavities, to fail to relieve abdominal distention from other causes, to neglect the value of deep breathing, to allow extremities to become cold, or to fail to see that gravity and muscular exercise are all highly important means of securing and maintaining normal venous flow from the legs. One need not be so concerned about the arms, for unless the patient is extremely weak the upper extremities will be moved to some extent. But, all too often, the legs are forgotten and allowed to remain motionless, or even worse, are propped up on pillows in a position most comfortable to the patient but dangerous to his welfare.

We believe, in common with many others, that the only sensible approach to the problem of pulmonary embolism is that of prevention of phlebothrombosis whenever the patient is seen from the onset of illness or injury, unless there are very definite contraindications. Comparatively few patients must be kept at absolute bed rest.

One of the first hurdles to clear is the old view that only surgical, accident, and obstetrical patients ever have pulmonary embolism. Nothing could be farther from the truth, as others and ourselves have amply proved. The common denominator in phlebothrombosis and pulmonary embolism is *confinement to bed*. The reason for going to bed is unimportant.

Another step that must be taken if progress is to be made is that of education of medical students, interns, physicians in practice, and nurses. Hereafter the teaching must be that all adults confined to bed are potential subjects of phlebothrombosis and pulmonary embolism. Nursing supervisors, out of training long enough not to have been taught the newer facts, must be so informed. These women stand in a crucial position, for upon their wholehearted cooperation largely depends the success or failure of any regime of treatment. Periodically in every hospital someone should give lectures and demonstrations both to the nurses and to the interns so that with changes in personnel the matter is not forgotten or allowed to lapse.

A simple means of making the hospital "embolism conscious" and of serving as a constant reminder that something is being done to prevent embolism is to hand stamp in large letters on the order sheet of

every chart the words *leg exercises: yes----* or *no-----*. Both the stamping and the check mark at the proper point are quickly done and save time. Printed letters are also much easier to read than longhand.

We do not know just how many times each day a bed patient should flex and extend the feet, knees, and thighs, but one thing is certain, namely, that some of the periods of exercise should be made in the presence of the nurse or physician. A convenient time for both is when the temperature is being taken, or at mealtimes. In this way the nurse can observe whether the patient is putting any effort into the exercise or merely playing at moving. Likewise, the intern and the resident should ask the patient to demonstrate his ability to exercise every time rounds are made.

If the cooperation of the patient is to be had, bed exercises must be made comfortable to him. One cannot expect a person to flex vigorously and extend the legs while tightly covered by bed clothing. Many people object to the scratchy sensation of their toenails against the bed sheet and will not move freely under such circumstances. Turning on one side easily obviates the difficulty.

Pillows under the knees for more than a very few minutes at a time should be an absolutely forbidden practice in all hospitals. At best the popliteal space is an anatomic bottleneck and to increase it by flexion and elevation of the knee is wholly unjustifiable.

The modern practice of early rising after operation and the shortening of confinement to bed of medical patients brought about by chemotherapy are undoubtedly doing something to prevent phlebothrombosis, but we must never forget that the process can begin within a very few days so that early rising alone will not insure against thrombosis.

In a recent thought-provoking symposium, Dock and his associates¹⁴ have emphasized not only the frequency of pulmonary embolism originating from leg and pelvic veins of bedridden persons, but other serious effects of confinement as well. His indictment of the abuse of bed rest is a scathing one.

Strange as it may seem, elevation of the head of the bed will effectually cause most patients to exercise their legs. All but the most debilitated have an innate dislike for slipping downward in bed and in bringing themselves back to the head of the bed are forced to put real effort into their legs. When nurses are insufficient, or where patients must be alone, this method has much to commend it.

While it has been shown that thyroid extract will increase metabolism and the circulation time, we have always felt it better to rely on purely physiologic means and not to risk upsetting the balance of the thyroid gland by giving the extract.

SUMMARY

1. A comparative study of the incidence of venous thrombosis of the legs in 400 unselected autopsies on adults, performed in the same hospital, before and after instituting preventive measures is presented.

2. In the last 200 cases dissection of the femoral and adductor veins was carried out. Like others who have examined the femoral vein, we find that phlebothrombosis of the lower extremities begins in the deep vessels of the calf and tends to propagate toward the heart, and that thrombosis of the femoral veins alone is an uncommon occurrence. Both sets of veins are the most frequent, and for this reason the most important, of all the possible sources of both fatal and nonfatal pulmonary emboli.

3. There were no important differences between the two series concerning age, sex, or location of the thrombosed calf veins. The last-mentioned feature has been considered in some detail in a previous publication.⁹

4. Thrombosis of the deep veins of the leg is a frequent event in all classes of middle-aged and older patients who for any reason whatsoever must go to bed for longer than a very few days. The onset is insidious and without prominent symptoms. Phlebitis, as a cause or as a complication of deep extremity vein thrombosis, is very uncommon and for this reason is unimportant.

5. The logical approach to the problem of phlebothrombosis and pulmonary embolism is prophylactic. Hitherto, in our opinion, there has been far too much emphasis upon diagnosis and treatment and too little on prevention.

6. Prophylaxis is best based on simple and readily carried out physiologic principles.

7. Re-education of physicians and nurses with respect to the seats and causes of thrombosis of the legs is urgently needed.

8. The incidence of phlebothrombosis in a small series of medical patients proved to be significantly less than it was in the first 200 cases. It seems probable that the institution of active exercises for this group is responsible for the decrease.

REFERENCES

1. Ochsner, Alton, and DeBakey, Michael: Thrombophlebitis and Phlebothrombosis, The C. Jeff Miller Lecture, *South. Surgeon* 8: 269-290, 1939.
2. Frykholm, Ragnar: The Pathogenesis and Mechanical Prophylaxis of Venous Thrombosis, *Surg., Gynec. & Obst.* 71: 307-312, 1940.
3. Denecke, K.: Der Plantarschmerz als Frühsymptom einer beginnenden Thrombose der unteren Extremität. *München. med. Wchnschr.* 76: 1912-1913, 1929. (Cited by Frykholm.²)
4. Olov, J.: Sur en détail concernant le diagnostic de la thrombose crurale, *Acta obst. et gynec. Scandinav.* 10: 159-162, 1930. (Cited by Frykholm.²)
5. Homans, John: Thrombosis of the Deep Veins of the Lower Leg, Causing Pulmonary Embolism, *New England J. Med.* 211: 993-997, 1934.
6. Rössle, R.: Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen, *Virchow's Arch. f. path. Anat.* 300: 180-189, 1937.
7. Neumann, R.: Ursprungszentren und Entwicklungsformen der Bein-Thrombose, *Virchow's Arch. f. path. Anat.* 301: 708-735, 1938.
8. Putzer, Rita: Die Wadenvenen Thrombose in ihrer Beziehung zur Architektur der Wade, *Arch. f. Gynäk.* 169: 444-452, 1939.
9. Hunter, Warren C., Sneed, Vinton D., Robertson, Thomas D., and Snyder, George A. C.: Thrombosis of the Deep Veins of the Legs; Its Clinical Significance as Exemplified in Three Hundred and Fifty-one Autopsies, *Arch. Int. Med.* 68: 1-17, 1941.

10. Smith, L. A., and Allen, E. V.: Vascular Clinics; XIV. Studies on the Rate of Venous Blood Flow; Physiologic Studies and Relation to Postoperative Venous Thrombosis and Pulmonary Embolism, *Proc. Staff Meet., Mayo Clin.* 16: 53-57, 1941.
11. Potts, Willis J., and Smith, Sidney: Pulmonary Embolism; An Experimental Study of Variations in the Volume Blood Flow in the Inferior Vena Cava of the Dog, *Arch. Surg.* 42: 661-664, 1941.
12. Luckhardt, Arno B., Alpert, Ruth, and Smith, Sidney: Hemodynamic and Respiratory Changes Following Manipulation and Traction of the Gastrohepatic Ligament, *Science* 76: 545, 1932.
13. Simpson, K.: Shelter Deaths From Pulmonary Embolism, *Lancet* 2: 744, 1940.
14. Dock, William: The Use and Abuse of Bed Rest; Conferences on Therapy, New York Hospital, New York State J. Med. 44: 724-730, 1944.

POSTOPERATIVE PULMONARY EMBOLISM

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PULMONARY embolism commonly is considered an unexpected catastrophe occurring suddenly after some operative procedure, and usually without warning, in a person who had convalesced nicely and was about to be discharged. Often the embolism takes place when the patient is just beginning to resume normal activities, for example, walking or at stool. This conception is only partially true, because embolism is perhaps even more frequent in persons who have been confined to bed for other reasons than an operation, as after delivery, a fracture, particularly of a lower extremity, and in many diseases, especially those associated with an impaired circulation. It may also, on rare occasions, occur in an individual who has not been confined to bed. In many instances there have been warnings as to what might happen—symptoms which, properly considered, might have led one to suspect that a small nonfatal embolism had taken place; for example, such symptoms as a sudden pleuritic pain with or without bloody sputum. Belt³ and Breslich⁴ have shown that pulmonary embolism is even more common in persons dying of medical diseases than in those dying after some operation and is present in some 10 to 12 per cent of routine post-mortem examinations on adults.

In 1846, Virchow¹⁰ published the first correctly interpreted examples of clot embolism of the lungs. Others, previously, had given clear descriptions of it, but did not correctly interpret or understand what had happened. Virchow's idea, that the clot, found obstructing the pulmonary artery, had come from the veins of the pelvis or lower extremities, was bitterly disputed for a long time. He^{10a} put his theory to the experimental test and proved that solid masses could be carried by the blood through the veins to the lungs. His cases of embolism occurred, as might be expected, not after operations, but following childbirth, trauma, and disease. When Virchow first wrote on this subject there were none of the present-day surgical procedures except amputations, hence it was not until some decades later that pulmonary embolism began to be considered a postoperative complication or accident. Then its occurrence in nonoperative patients was forgotten to a degree and the broader aspects of the whole problem did not receive deserved attention; in discussion, embolism was, to a great extent, regarded as a surgical calamity. In the century since Virchow gave his clear description, even though papers without number have been written on the subject, much is still to be learned about the underlying causes of thrombosis and embolism and their prevention.

Pulmonary embolism is always a complication of some pre-existing disease, which has almost always confined the person to bed. When the embolism takes place the symptoms usually come on suddenly. Depending largely upon the size of the embolus or emboli, death occurs quickly, after some minutes, hours, or days. Probably not infrequently the patient recovers completely. The symptoms, in brief, are dyspnea, substernal pain or discomfort, cyanosis, and anxiety. There may be a pleuritic type of pain, vomiting or cerebral symptoms, sometimes with convulsions, or signs of shock and circulatory collapse. If the embolus is massive, occluding the trunk of the pulmonary artery, it may kill in a few seconds. If small, one or more lung infarcts may develop, with or without pleural pain, effusion, or bloody sputum. Infarction often precedes a final fatal embolism. A shower of small emboli may have the same effect as a single large one, interfering either with the free access of blood to the lung, resulting in damage to the lung, or by stasis to the brain. When there is a shower of small emboli, all of them probably do not reach the lung at the same time, but the end result may be the same, although the time from onset to death will probably be much greater. If there is a series of small embolisms, some of the earlier ones to arrive in the lungs may cause infarctions or propagate proximally and bring about the same result as a single large embolus. With an embolism, which is not immediately fatal, pneumonia or coronary disease is often suspected. When either pneumonia or a coronary attack is diagnosed in a convalescent, one should remember that a nonfatal embolism may be the correct diagnosis. Such symptoms may constitute a warning of a fatal embolism to come. McGinn and White¹⁴ and others have shown that by the use of electrocardiography a differentiation may be made between coronary disease and acute cor pulmonale.

Before pulmonary embolism can take place there must be thrombosis of a vein in some part of the body. The common primary sites of thrombosis are the veins of the lower extremities and pelvis, and rarely elsewhere. Small nonfatal emboli not infrequently come from the right side of the heart, usually from the atrium. Embolism usually occurs in individuals who have shown none of the ordinary signs of thrombophlebitis. An unexplained fever or leucocytosis may be the only indication that something is wrong. When an embolus is found at post-mortem examination, one is immediately curious as to its origin. As necropsies are ordinarily done, the site of primary thrombosis is found in only about two-thirds of examinations, although a complete dissection may fail to reveal the source. Perhaps in such instances the entire thrombus had torn loose and a small roughened area on the intima of a vein might be overlooked easily. Massive emboli usually come from the iliac or femoral veins, although the very beginning of the thrombus may have been far down the leg. Hunter and his co-workers¹¹ have shown at post-mortem examination that in bed patients

in the latter half of life, thromboses are present in the deep veins of the leg in 52.7 per cent of cases. Rössle¹⁷ has found such thrombosed veins in approximately 25 per cent of adults at necropsy. It is often alleged that the primary site of thrombosis is more frequently in the left than the right lower extremity, but there is reason to doubt the truth of this statement. It rarely happens that an embolus has its origin in a vein in the field of operation. When pulmonary embolism occurs after trauma the primary thrombosis may have been in a traumatized vein, but not necessarily so, as it may have arisen in the opposite extremity. In embolism following delivery, the embolus may have come from a vein near the uterus, but again not necessarily so.

The process of thrombosis is closely related to the normal process of coagulation of blood, but normally there is no intravascular clotting during life. If blood did not normally clot after a blood vessel was opened, there could be no successful surgery, because hemorrhage could not be completely stopped, and people would die after trivial cuts. In patients who develop thrombosis, with or without embolism, clotting of the blood goes far beyond the normal limits, and clots form where there has been no obvious injury to a vessel. Why this abnormal clotting takes place is not entirely clear. Many factors apparently operate to cause thrombosis. Usually these factors are divided into three groups: (1) slowing of the blood stream, (2) injury of the endothelium, and (3) changes in the composition of the blood. Which of these is most important we do not know; probably in a given instance one is more important than the others. Slowing of the blood stream, particularly with eddy formation, has long been considered as of prime importance. In my material, venous thrombosis was found five to six times as commonly where chronic passive congestion, as indicated by the liver, was present, as when there was no passive congestion. It is well known that when endothelium is damaged thrombosis may occur. Group 3, changes in the composition of the blood, includes many items, for example, changes in the prothrombin time, clotting time, calcium time, sedimentation rate, platelet count, infection. There are other factors of importance which cannot be placed in any of these groups. These are age, sex, site of operation or injury, disease, obesity, and weather. Advancing age with its gradual loss of muscular tone and relative inactivity may well cause some slowing of the blood stream, even though there is no apparent organic cardiovascular disease. Obesity, likewise, may decrease the rate of flow of the blood stream for the same reasons as advancing age. Enforced bed rest from any cause may slow the blood stream, especially in certain parts of the body. Disease through inactivity or changes in the composition of the blood might promote stasis and thrombosis. An old person with impaired muscular tone and cardiovascular system should be a much more likely candidate for thrombosis and embolism than a young person with good muscular tone and a sound cardiovascular system, if

each was subjected to the same operation or trauma. If advanced age, obesity, impaired cardiovascular system, disease, and operation occur in the same person the likelihood of thrombosis may be still greater. It would appear that thrombosis and embolism may be due to a number of variables, operating in different combinations in different persons.

Aschoff's¹ theory of thrombosis is the one most generally accepted, although in recent years some opposition to it has arisen. According to Aschoff, fatal emboli come from thromboses of the iliac or femoral veins. The thrombus usually begins near a vein valve as a platelet or agglutination thrombus and this forms the head or *Kopfteil*. When this platelet thrombus has become large enough to occlude the vein, then a coagulation thrombus made up of fibrin, red blood cells, and leucocytes forms in the obstructed vein where the blood is at a standstill. In recent years, due to the studies of Olow,¹⁶ Denecke,⁶ Rössle,¹⁷ Neumann,¹⁵ Frykholm,⁸ and others, evidence has accumulated indicating that the thrombosis, with or without embolism, actually may have started in the deep veins of the calf of the leg or foot. Then by propagation and accretion the thrombus may have extended up the veins of the lower extremity, not occluding the lumens, but waving freely in the passing blood. It has been suggested that compression of the veins during rest in bed may have caused empty veins to be flattened and the so-apposed endothelial linings to be damaged. Such a focus of endothelial injury might be the site for the initiation of a thrombus.

It is very difficult to work out the real incidence of thrombosis and embolism for many reasons. Autopsy material should give accurate information on this subject, if complete post-mortem examinations were done routinely. Unfortunately, necropsies are done on only a fraction of those who die in any community or hospital, and at best give information only on those examined. Hospital populations vary from hospital to hospital in age, sex, type of disease, economic status, etc.

Reports from various sources show an incidence of from less than 1 to almost 12 per cent in routine autopsies. Domrich⁸ in 26,439 necropsies found pulmonary embolism in one-half of 1 per cent and in another series of 2,500 examinations an incidence of 2.4 per cent. Belt³ in 567 examinations found emboli in 9.8 per cent of persons and Breslich⁴ in 457 necropsies found embolism in 11.8 per cent. A serious difficulty encountered in trying to compare the data of different authors is that often the age distribution of all the patients on whom post-mortem examinations were made is not given. A series derived from nonsurgical deaths cannot be compared with a series from a surgical service. Another difficulty found in trying to make comparisons is that many authors have drawn no distinction between fatal and non-fatal embolisms. The incidence of thrombosis and embolism based entirely on clinical data is open to obvious objections.

Similarly in reports on the incidence of thrombosis and embolism following surgical procedures, there is great variation ranging from 0.02 to almost 1 per cent. In 1912, Wilson²⁰ reported on 63,753 operations done at the Mayo Clinic and found an incidence of embolism of 0.07 per cent. Heard,¹⁰ in 1923, at the Mayo Clinic found an incidence of embolism of 0.12 per cent in 60,757 operations on men and of 0.07 per cent in 43,605 operations on women. In 1940, Barker and his collaborators,² also reporting from the Mayo Clinic, showed an incidence of thrombosis and embolism of 0.96 per cent in 172,888 operations, of pulmonary embolism of 0.52 per cent, and of fatal embolism of 0.20 per cent. They have analyzed their material according to site of operation and magnitude. They found that the incidence of fatal pulmonary embolism varied from 0 to 0.77 per cent. All of these series have come from the same clinic and yet there is a difference in incidence. It might appear that these series are really comparable, but yet they may not be at all similar. It might appear that embolism had increased in frequency at the Mayo Clinic, but it is doubtful whether such a conclusion is really justified.

Numerous articles have been written to show that thrombosis and embolism have increased since World War I. Part of this apparent increase can probably be referred to comparisons of dissimilar data. From perusal of articles written since Virchow's description it would appear that the incidence of embolism has followed a wavelike course. Virchow reported one of the highest incidences of embolism, having found pulmonary embolism eleven times in seventy-six post-mortem examinations.

My data are based on 25,771 necropsies done by the department of pathology of the University of Minnesota during the twenty years from Jan. 1, 1919, to Dec. 31, 1938. From the autopsy records I determined that in 689 instances, or 2.67 per cent, death was to be attributed to pulmonary embolism. This appears to be but one-fourth the incidence as determined by Belt and Breslich. However, in my opinion this difference in incidence is to be explained by the fact that they were considering all pulmonary embolisms, fatal and nonfatal. Their conception, while broader than mine, is still not broad enough. To get a full view of the problem we must broaden the base to include not only the cases where pulmonary embolism actually occurred, but also those instances where it might have taken place, because venous thrombosis was present. The embolism was merely a fortuitous event. When a thrombus forms in a vein, the bearer of that vein is in line to be a victim of pulmonary embolism. From this point of view there was, in my material, embolism or the possibility of embolism in 10 per cent of the autopsies. If the cases of venous thrombosis without embolism be deducted, then pulmonary artery thrombosis or embolism occurred in 7.2 per cent, a figure not too far from those of Belt and Breslich. The difference may be due to differences in the sources from

which the material was obtained. My material came from private and charity hospitals, the coroner's service, and the private practices of physicians. It represents about 16 per cent of the deaths in Minneapolis, but included are necropsies done on persons who had died elsewhere. The age distribution in these examinations closely follows the curve of vital statistics as to decade distribution of deaths.

Much has been written to show that pulmonary embolism has a seasonal incidence. De Takats and his co-workers⁷ studied 100 cases of pulmonary embolism and found the greatest incidence during the spring and fall, the times of the year with the greatest fluctuations in barometric pressure and temperature. Martland¹² found that in 86 massive embolisms in 10,797 necropsies from his medical examiner's service, March, April, September, and December were the months with the greatest incidence of pulmonary embolism. My material covering a twenty-year period shows that month by month and year by year the number of examinations runs at a fairly uniform level, although the number of examinations has gradually increased. The incidence of thrombo-embolism has also followed a uniform course and there are no indications of a seasonal influence.

Consideration of the decade distribution of the present series of post-mortem examinations and the occurrence of thrombo-embolism in the various decades showed that thrombosis and embolism occurred at all ages with a tendency to a greater incidence as age advanced. This was true whether fatal embolism or venous thrombosis with or without embolism was considered. This effect of age is shown in Table I and particularly with fatal embolism there is a steady rise from the first to the ninth decades. Perhaps the frequency of thrombosis in the first decade may be referred to infections, such as those of the middle ear. Puerperal infection doubtless increases the incidence of thrombo-embolism during the childbearing period, although fatal embolism after delivery is infrequent. Nevertheless, fatal pulmonary

TABLE I

AGE DISTRIBUTION OF 25,771 NECROPSIES AND INCIDENCE OF THROMBO-EMBOLISM AND FATAL EMBOLISM IN EACH DECADE

DECADE	NUMBER	THROMBO-EMBOLISM (PER CENT)	FATAL EMBOLISM (PER CENT)
1	3,277	3.1	0.18
2	1,050	9.7	0.57
3	1,945	9.4	1.49
4	2,676	9.0	2.09
5	3,818	10.6	2.46
6	4,157	12.2	3.31
7	4,196	12.4	3.95
8	2,908	14.1	4.74
9	816	13.6	5.39
10	54	12.9	1.84
Adults	874		
Total	25,771	10.1	2.67

embolism is notably higher in women after delivery than in those dying during the childbearing period.

From earlier studies¹³ it appeared that fatal embolism was more common in men, but after fatal trauma more common in women. Barker and co-workers found thrombosis and embolism to be relatively more common in women than in men, but fatal embolism more frequent in men. The present study indicates that thrombo-embolism and fatal embolism are more common in women, thrombo-embolism occurring in 9.1 per cent of men and in 11.2 per cent of women, and fatal embolism in 2.2 per cent of men and 3.3 per cent of women. (In this calculation post-partum cases were excluded, because of this special condition.)

In order to study another factor which might play a part in thrombo-embolism, this material was divided according to anatomically normal and abnormal hearts. This analysis showed that in persons with heart disease, thrombosis and embolism occurred approximately three times as often as it did in persons with normal hearts. Further subdivision of these two groups by age revealed that in persons with anatomically normal hearts there was a slight but gradual increase of thrombosis and embolism as age advanced, whereas in persons with diseased hearts thrombo-embolism occurred fairly uniformly in all decades of life, except the first. As just indicated, when the liver showed chronic passive congestion, venous thrombosis was five to six times as common as it was when the liver appeared normal.

Thrombo-embolism may be divided readily into postoperative, post-traumatic, post-partum, and medical groups. When thus divided I found, for these groups, incidences of 5.4, 3.5, 4.7, and 1.2 per cent respectively. A statistical determination of the significance of these differences in percentage has not been made. In all of these four groups, when divided according to age, there appeared to be a definite age effect, with an increasing occurrence of thrombo-embolism with advancing age.

A discussion of postoperative thrombosis and embolism, to which objections cannot be raised, requires much more data than are usually given. It is necessary to know not only the number of operations according to sites, but also the sex, the ages at which the various operations have been done, the postoperative mortalities by decades, and, if post-mortem examinations were not made, then the clinical causes of death should be included. Such information I have not as yet been able to find. This information is needed before there is justification for claiming that certain operations are more likely than others to be followed by thrombo-embolism. It may be true, but the reasons and the foundations for the statements do not appear. To state that pulmonary embolism occurs more commonly after certain operations and in the latter half of life is a commonplace, but this truism is usually not investigated further and the reasons and causes

for any such greater occurrence have not been found. Among the contributors to the higher incidences of pulmonary embolism are mentioned operations on the bladder and prostate. A moment's reflection suggests that the reason for this may be that such operations are done only rarely in the early decades of life. It is often said that appendectomy is a large contributor to embolism in early life. The obvious reason for this is that most of the primary appendectomies are done during the first three decades of life and with the large numbers of appendectomies done, the chances for embolism to occur are increased, even though the actual incidence may be very low. Why herniorrhaphy should so often, as is alleged, be followed by thrombosis or embolism is not clear, but, as in the case of the appendix, it may be related to the time of life when most hernioplasties are done.

Barker and his collaborators, in their study of 172,888 operations, divided them according to site and magnitude of operation. They found "venous thrombosis and pulmonary embolism are relatively twice as common following laparotomy as they are following all operations and they are three times as common following laparotomy in which operations on the female pelvic organs were done as they are following all operations. The highest incidence of venous thrombosis and pulmonary embolism occurs in operations where there is laparotomy and extensive resection of tissue. These are operations which can be considered to be of relatively long duration and of relatively great magnitude. The incidence of venous thrombosis and pulmonary embolism is approximately twice as great in cases of repair of bilateral femoral or inguinal hernia as in cases of unilateral femoral or inguinal hernia. Here the difference is only that of magnitude and duration of operation." They call attention to the high incidence after splenectomy, and believe it is in some way related to the blood changes associated with the reasons for splenectomy. Their data are tabulated under four heads, namely, all thrombosis and embolism, pulmonary embolism, fatal pulmonary embolism, and clinical diagnosis of thrombophlebitis. Rearrangement of these data gives some interesting results. Splenectomy takes first place three times in these four items and second place once. Abdominal hysterectomy takes first place, once; second place, twice; and sixth place, once. Third place is taken twice by cesarean section and once each by resection of the intestine and other intestinal operations. Fourth place is taken once by other intestinal operations, once by bladder and prostate operations, once by exploratory laparotomy for inoperable malignant lesion, and once by bilateral femoral or inguinal hernia operations. Twice colostomy and/or enterostomy assumes fifth place, and once each this place is taken by bilateral femoral or inguinal hernia and vaginal hysterectomy. Sixth place falls twice in the column of resection of the stomach and once each in abdominal hysterectomy and other intestinal operations. Seventh place is taken once each by cesarean section, bilateral femoral or inguinal hernia operation, intestinal resection, and other gynecologic operations.

Eighth place falls once in the column of vaginal hysterectomy, once in appendectomy for ruptured appendix, once in bilateral femoral or inguinal hernia, and once in other hernia except diaphragmatic. Ninth place is twice in the column for resection of the stomach, once in prostate and bladder, and once in colostomy or enterostomy. In tenth place are colostomy or enterostomy, exploratory laparotomy for inoperable malignant lesion, other lower abdominal operations, gall bladder and duct, and other stomach operations. This survey might be continued through all the thirty-six types or locations of operations tabulated by the authors. This much reveals that thrombo-embolic disease tends to occur particularly after operations on special sites, without any apparent explanation, save that, with the exception of vaginal hysterectomy, the chief contributors involved incision into or through the anterior abdominal wall. Their table also shows that no part of the body was free of its complement of postoperative thrombo-embolism. Culp,⁵ in a survey of 8,163 urologic operations, found 88 pulmonary embolisms of which 32 were fatal and so proved at necropsy. There were 11 presumptive embolisms, 21 infarcts with recovery, and 4 infected infarcts. He states that embolism was responsible for 6.62 per cent of all postoperative deaths. He also noted that 81.2 per cent of the embolisms were in private patients, and the only difference between private and ward patients that he could find was that the former tended to be overweight and the latter underweight. Of the embolisms, 62.5 per cent were in persons over 60 years of age, whereas only 41.2 per cent of all patients were over 60 years of age. Further, while 25 per cent of fatal embolisms were in persons from 71 to 80 years of age, only 12.5 per cent of all patients were of this age. Of the patients with embolism, 31 per cent were of normal height, 43.7 per cent underweight, and 25 per cent overweight. The incidence of fatal embolism after suprapubic operations was 0.67 per cent, after perineal 0.57 per cent, and after transurethral 0.25 per cent. There was marked abdominal distention in 43.8 per cent, which might have increased stasis of blood in the pelvis or lower extremities. There was clinical evidence of cardiac decompensation preoperatively in 20 per cent, another 10 per cent had high diastolic pressures, and another 40 per cent had myocardial scarring at post-mortem examination. Clinical thrombosis was present in 18.8 per cent. Veal,¹⁸ in a study on femoral vein ligations to prevent pulmonary complications after thigh amputations, concludes that "pulmonary complications are more frequent following thigh amputations than in any other field of surgery. Many of the pulmonary lesions are embolic in origin." All of these indicate that it is necessary to know more about the operative procedures than their site and magnitude. Knowledge as to age at which operations are done as well as mortality by decades might furnish useful information in an attempt to learn the factors which underlie thrombo-embolism.

To get some information on the question of when various operations are done, I have gathered from the literature data bearing on this point. These data show that for the appendix about three-fourths of the primary appendectomies are done before the age of thirty years; about one-half of the herniorrhaphies are done during the first three decades; about 85 per cent of gall bladder operations are done after the age of 30 years, more than one-half between the ages of 30 and 49 years, and less than one-third after the age of 50 years. Apparently about one-half of the abdominal gynecologic operations are done during the fourth and fifth decades, and only about 20 per cent after the age of 50 years: until the fifth decade there are almost no suprapubic operations on the bladder and prostate; about 75 per cent of operations on the head and neck are done during the first three decades of life. This by no means covers all the operative fields, but is a clear indication that age must be given full consideration before a true comparison can be made as to the relative incidence of thrombo-embolism as a complication following operations on particular sites.

Of the 25,771 autopsy records studied, I decided that 4,070 were to be classified as postoperative deaths. In this group venous thrombosis or pulmonary embolism was found in 471 instances or in 11.5 per cent. I considered that in 216 instances the pulmonary embolism could be called fatal, that is, in 5.3 per cent of cases. There were 1,506 women with 182 thromboses and embolisms, or 12.0 per cent, and 2,564 men with 281 instances of thrombo-embolism, or 10.9 per cent. In the 1,506 women there were 90 fatal embolisms, or 5.9 per cent, and in the 2,564 men 126 fatal embolisms, or 4.9 per cent.

Table II indicates that the ages in the routine autopsies and in those done after postoperative deaths are approximately the same. The actual number of autopsies in each decade done on persons dying after operation is given at the end of Table III. In the same place are given the incidences of thrombo-embolism and fatal embolisms. If it may be assumed that such distribution of postoperative deaths is true, then it is clear that while thrombosis and embolism occur in all decades there is a tendency for them to increase in frequency with age. This is even truer of fatal embolism. It is worthy of note that only 11, or

TABLE II
AGE DISTRIBUTION OF AUTOPSIES (24,927 ROUTINE AND 4,040 POSTOPERATIVE)

DECADE	ROUTINE	POSTOPERATIVE
1	13.1	10.2
2	4.2	5.5
3	7.8	7.4
4	10.7	10.0
5	15.3	12.4
6	16.6	13.6
7	16.8	13.5
8	11.6	11.6
9	3.2	2.4

5 per cent, of the 214 fatal embolisms considered as fatal occurred in patients before the age of 30 years, and that only 31, or 14.4 per cent, were in persons under 40 years of age, whereas 23.2 per cent of all postoperative thromboses and embolisms were in persons under 40 years of age.

Table III shows the age, site of operation, and incidence of thrombo-embolism and fatal embolism, in the 4,070 necropsies in persons dead after operation. The operative sites were associated with thrombo-embolism and fatal embolism in the actual numbers as shown in Table IV, and the incidence of thrombo-embolism and fatal embolism as complications of these various sites is shown in Table V. (In these tables suprapubic operations on the bladder and/or prostate are all included under bladder, and the transurethral prostatectomies under perineum.)

The relatively high incidence of thrombosis, with or without embolism, after operations on the head is doubtless related to infection, for example, otitis media and mastoiditis. It may be noted in Table III that of the 391 operations on the head, 165 were done in patients under the age of 20 years and 207 in those under the age of 30. Of the fifty-eight instances of thrombo-embolism after head operations thirty-three were in persons under 30 years of age. All of these thirty-three were associated with infection. There were five fatal embolisms after head operations and all were in persons over 50 years of age. These five embolisms give an incidence of 1.2 per cent for persons dying after head operations. Operations on the extremities were the second largest contributor to the actual number of instances of thrombo-embolism, but ranked in eighth place in the number of fatal embolisms. Fatal embolism occurred in only 5.5 per cent of persons, but the possibility of embolism was present in 20 per cent. It is to be noted in Table III that thrombo-embolism and fatal embolism occurred in all but two of the decades (third and fifth), and that here there is no evidence of an increased incidence with age.

Suprapubic operation on the bladder and/or prostate was in third place in the actual number of thrombo-embolisms and in second place in the number of fatal embolisms. Thrombo-embolism occurred with the possibility of fatal embolism in 15.5 per cent of persons and such fatal embolism took place in 10.3 per cent of individuals. In Table III it will be noted that no thrombosis or embolism was found before the fifth decade in any person who had undergone an operation on these organs, further that all the fatal embolisms occurred after the fifth decade of life. Of the 270 operations in this category, 9 were in women with neither thrombosis nor embolism. Of the twenty-eight fatal embolisms in men, all but one occurred after the sixth decade. Sixteen of these followed prostatectomy and twelve followed various operations on the bladder. Fifteen showed normal hearts and thirteen some evidence of organic heart disease. It may be mentioned here that in forty-one deaths following transurethral resection of the prostate there

TABLE III
AGE, SITE OF OPERATION, AND INCIDENCE OF THROMBO-EMBOLISM AND FATAL ENPHOLISM IN 4,070 POSTOPERATIVE NECROPSIES

	DECADE										TOTAL
	1	2	3	4	5	6	7	8	9	10	
<i>Sites</i>											
Head	110	55	5	38	42	39	32	19	5		391
T.E. %	10.0	21.8	23.8	13.1	14.2	15.4	9.3	22.2	20.0		14.8
Emb. %						2.5	6.2	5.2	20.0		1.2
Neck	53	12	11	27	32	46	51	21	3	2	258
T.E. %		25.0			15.5	15.2	3.5	9.5			7.3
Emb. %					3.1		7.9	4.7			1.1
Thorax	26	15	36	38	49	31	15	3	1		215
T.E. %		20.0	11.1	18.4	1.0	7.8	5.3				10.2
Emb. %			2.7	7.9		5.8					2.7
Spine	13	10	3	8	3	9	2	2	1		54
T.E. %					33.3						1.8
Emb. %											0
Expl. lyp.	52	17	34	53	75	87	81	11	3	6	450
T.E. %	3.8	11.7	5.5	3.7	4.0	6.8	8.6	2.4	33.3		5.7
Emb. %			2.9	1.8	1.3	3.4	3.7				2.0
Stomach	31		9	18	55	93	82	31	6	4	352
T.E. %				5.5	5.6	4.3	8.5	9.8	16.6		5.6
Emb. %						2.1	2.1	3.9	16.6		1.9
Small int.	8	9	13	38	48	40	11	20		2	233
T.E. %			7.6	7.8	10.4	10.7	4.5	10.0		1	7.6
Emb. %			7.6	7.2	4.1	2.5	2.2	5.0			4.0
Large int.	8	5	8	13	10	7	94	39	10		293
T.E. %			12.5	7.6	15.0	14.1	13.9	5.1			11.5
Emb. %					5.0	5.1	9.5	2.5			5.7
Gall bladder			15	27	56	74	77	30	1		280
T.E. %				7.4	14.2	8.1	11.6	10.0			10.0
Emb. %				3.7	10.7	6.7	10.3	6.6			7.8

Appendix	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200	201	202	203	204	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	223	224	225	226	227	228	229	230	231	232	233	234	235	236	237	238	239	240	241	242	243	244	245	246	247	248	249	250	251	252	253	254	255	256	257	258	259	260	261	262	263	264	265	266	267	268	269	270	271	272	273	274	275	276	277	278	279	280	281	282	283	284	285	286	287	288	289	290	291	292	293	294	295	296	297	298	299	300	301	302	303	304	305	306	307	308	309	310	311	312	313	314	315	316	317	318	319	320	321	322	323	324	325	326	327	328	329	330	331	332	333	334	335	336	337	338	339	340	341	342	343	344	345	346	347	348	349	350	351	352	353	354	355	356	357	358	359	360	361	362	363	364	365	366	367	368	369	370	371	372	373	374	375	376	377	378	379	380	381	382	383	384	385	386	387	388	389	390	391	392	393	394	395	396	397	398	399	400	401	402	403	404	405	406	407	408	409	410	411	412	413	414	415	416	417	418	419	420	421	422	423	424	425	426	427	428	429	430	431	432	433	434	435	436	437	438	439	440	441	442	443	444	445	446	447	448	449	450	451	452	453	454	455	456	457	458	459	460	461	462	463	464	465	466	467	468	469	470	471	472	473	474	475	476	477	478	479	480	481	482	483	484	485	486	487	488	489	490	491	492	493	494	495	496	497	498	499	500	501	502	503	504	505	506	507	508	509	510	511	512	513	514	515	516	517	518	519	520	521	522	523	524	525	526	527	528	529	530	531	532	533	534	535	536	537	538	539	540	541	542	543	544	545	546	547	548	549	550	551	552	553	554	555	556	557	558	559	560	561	562	563	564	565	566	567	568	569	570	571	572	573	574	575	576	577	578	579	580	581	582	583	584	585	586	587	588	589	590	591	592	593	594	595	596	597	598	599	600	601	602	603	604	605	606	607	608	609	610	611	612	613	614	615	616	617	618	619	620	621	622	623	624	625	626	627	628	629	630	631	632	633	634	635	636	637	638	639	640	641	642	643	644	645	646	647	648	649	650	651	652	653	654	655	656	657	658	659	660	661	662	663	664	665	666	667	668	669	670	671	672	673	674	675	676	677	678	679	680	681	682	683	684	685	686	687	688	689	690	691	692	693	694	695	696	697	698	699	700	701	702	703	704	705	706	707	708	709	710	711	712	713	714	715	716	717	718	719	720	721	722	723	724	725	726	727	728	729	730	731	732	733	734	735	736	737	738	739	740	741	742	743	744	745	746	747	748	749	750	751	752	753	754	755	756	757	758	759	760	761	762	763	764	765	766	767	768	769	770	771	772	773	774	775	776	777	778	779	780	781	782	783	784	785	786	787	788	789	790	791	792	793	794	795	796	797	798	799	800	801	802	803	804	805	806	807	808	809	810	811	812	813	814	815	816	817	818	819	820	821	822	823	824	825	826	827	828	829	830	831	832	833	834	835	836	837	838	839	840	841	842	843	844	845	846	847	848	849	850	851	852	853	854	855	856	857	858	859	860	861	862	863	864	865	866	867	868	869	870	871	872	873	874	875	876	877	878	879	880	881	882	883	884	885	886	887	888	889	890	891	892	893	894	895	896	897	898	899	900	901	902	903	904	905	906	907	908	909	910	911	912	913	914	915	916	917	918	919	920	921	922	923	924	925	926	927	928	929	930	931	932	933	934	935	936	937	938	939	940	941	942	943	944	945	946	947	948	949	950	951	952	953	954	955	956	957	958	959	960	961	962	963	964	965	966	967	968	969	970	971	972	973	974	975	976	977	978	979	980	981	982	983	984	985	986	987	988	989	990	991	992	993	994	995	996	997	998	999	1000	1001	1002	1003	1004	1005	1006	1007	1008	1009	1010	1011	1012	1013	1014	1015	1016	1017	1018	1019	1020	1021	1022	1023	1024	1025	1026	1027	1028	1029	1030	1031	1032	1033	1034	1035	1036	1037	1038	1039	1040	1041	1042	1043	1044	1045	1046	1047	1048	1049	1050	1051	1052	1053	1054	1055	1056	1057	1058	1059	1060	1061	1062	1063	1064	1065	1066	1067	1068	1069	1070	1071	1072	1073	1074	1075	1076	1077	1078	1079	1080	1081	1082	1083	1084	1085	1086	1087	1088	1089	1090	1091	1092	1093	1094	1095	1096	1097	1098	1099	1100	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	1111	1112	1113	1114	1115	1116	1117	1118	1119	1120	1121	1122	1123	1124	1125	1126	1127	1128	1129	1130	1131	1132	1133	1134	1135	1136	1137	1138	1139	1140	1141	1142	1143	1144	1145	1146	1147	1148	1149	1150	1151	1152	1153	1154	1155	1156	1157	1158	1159	1160	1161	1162	1163	1164	1165	1166	1167	1168	1169	1170	1171	1172	1173	1174	1175	1176	1177	1178	1179	1180	1181	1182	1183	1184	1185	1186	1187	1188	1189	1190	1191	1192	1193	1194	1195	1196	1197	1198	1199	1200	1201	1202	1203	1204	1205	1206	1207	1208	1209	1210	1211	1212	1213	1214	1215	1216	1217	1218	1219	122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TABLE IV

ACTUAL NUMBERS OF THROMBO-EMBOLISMS AND FATAL EMBOLISMS ACCORDING TO OPERATIVE SITES

THROMBOSIS AND EMBOLISM	NUMBER	FATAL EMBOLISM	NUMBER
Head	58	Hernia	20
Extremity	47	Bladder	28
Bladder	42	Gall bladder	22
Hernia	35	Appendix	19
Large intestine	34	Uterus	19
Appendix	33	Perineum	17
Perineum	33	Large intestine	16
Gall bladder	28	Extremity	13
Uterus	27	Small intestine	9
Exploratory laparotomy	26	Exploratory laparotomy	9
Thorax	22	Stomach	7
Stomach	20	Kidney	7
Neck	19	Thorax	6
Small intestine	17	Adnexa	6
Kidney	14	Head	5
Adnexa	8	Neck	3
Miscellaneous	7	Miscellaneous	1
Spine	1	Spine	0
Spleen	0	Spleen	0

whole Lawrence's instances of fatal pulmonary embolism among individuals with heart disease. This is an incidence of 17 per cent which is more than twice the incidence for the whole perineal group.

The 128 operations for hernia yielded the greatest number of fatal embolisms, and herniorrhaphies ranked first among the operative sites having this complication and cause of death. As will be seen in Table III, no thromboses or fatal embolisms occurred in patients under the age of 30 years and the highest incidences of thrombo-embolism and fatal embolism were found in the seventh decade of life.

TABLE V

INCIDENCE OF THROMBO-EMBOLISM AND FATAL EMBOLISM ACCORDING TO OPERATIVE SITES

THROMBO-EMBOLISM	PER CENT	FATAL EMBOLISM	PER CENT
Uterus	25.4	Hernia	22.6
Hernia	24.2	Uterus	17.9
Extremity	20.0	Bladder	10.3
Bladder	15.5	Gall bladder	7.8
Perineum	14.8	Perineum	7.6
Head	14.8	Adnexa	7.1
Kidney	12.8	Kidney	6.4
Large intestine	11.5	Appendix	6.1
Appendix	10.6	Extremity	5.5
Miscellaneous	10.2	Large intestine	5.4
Thorax	10.2	Small intestine	4.0
Gall bladder	10.0	Thorax	2.7
Adnexa	9.5	Exploratory laparotomy	2.0
Small intestine	7.6	Stomach	1.9
Neck	7.3	Miscellaneous	1.4
Exploratory laparotomy	5.7	Head	1.2
Stomach	5.6	Neck	1.1
Spine	1.8	Spine	0
Spleen	0	Spleen	0

Operations on the large intestine took fifth place in the list of possibilities for fatal embolism and seventh place in the number of fatal embolisms-actually produced. Thus, large intestinal operations had fatal embolism in 5.4 per cent of cases. In Table III it may be seen that there was no instance of fatal embolism, after operation on the large intestine before the fifth decade of life. The peak of incidence for thrombo-embolism was in the fifth decade and the peak for fatal embolism in the seventh decade.

Biliary tract operations produced the third greatest number of fatal embolisms and this was the cause of death in 7.8 per cent of persons after such operations. Thrombo-embolism and fatal embolism first appear in the fourth decade. The decades where these are found show no definite peak in any decade.

Uterine and appendiceal operations tie for fourth place in the number of fatal embolisms found, although the possibilities for fatal embolism might seem to have been greater for the latter than the former. This does not appear to be true, as is shown in Table V, where thrombo-embolism was present in 25.4 per cent of uterine operations and but 10.6 per cent of appendiceal operations. Likewise embolism was fatal in 17.9 per cent of the deaths following uterine operations and caused death in but 6.1 per cent after operations on the appendix. It is to be noted, in Table III, regarding the appendix, that embolism appeared first in the second decade and reached its peak in the seventh decade of life, whereas no fatal embolism after a uterine operation was observed until the fourth decade. In both instances there is evidence of an increased incidence of thrombo-embolism and fatal embolism with advancing age.

As may be seen from Tables III, IV, and V, thrombo-embolism and fatal embolism may follow operations on almost any part of the body, but the occurrence of these complications is less frequent than with those just discussed. Examination of Table III will show that for most parts of the body the incidences of thrombo-embolism and fatal embolism increase with the age of the patient.

While it may be correct to say that certain operations are those most likely to be followed by pulmonary embolism, inspection of Tables III, IV, and V will indicate that before such a statement is made certain information aside from the site of operation must be considered. Two of these other considerations are very definitely age and sex.

SUMMARY

A study of 25,771 autopsy records at the University of Minnesota has revealed that 4,070 of the deaths may be considered as postoperative. Among these, postoperative deaths there were 471 instances, or 11.5 per cent, where thrombo-embolism was present and 216, or 5.3 per cent, where it was believed that pulmonary embolism was to be considered as the cause of death.

TABLE I
NONFATAL POSTOPERATIVE PULMONARY EMBOLISM AND INFARCTION

	CONTROL GROUP: ANTICOAGULANTS NOT ADMINISTERED		DICUMAROL ADMINISTERED	
	NUMBER	PER CENT	NUMBER	PER CENT
Total cases	678	100	180	100
Subsequent venous thrombosis, pulmonary embolism, or infarction	297	43.8	2*	1.1
Subsequent fatal pulmonary embolism	124	18.3	1†	0.6

*Both when prothrombin was greater than 30 per cent.

†After prothrombin had returned to normal.

previous study⁷ is given in Table I. The difference in incidence is striking and, as indicated, there was no recurrence of thrombosis or embolism when the prothrombin deficiency was adequately maintained.

Thrombophlebitis.—In the group of cases in this study no attempt was made to distinguish between phlebothrombosis and thrombophlebitis, since we feel that although the lesion starts with a thrombus, some degree of phlebitis is also present when the diagnosis is made clinically. Some or possibly all of these cases might be classified as phlebothrombosis by those who attempt to make the distinction. Of the 138 cases of thrombophlebitis in which dicumarol was administered, the lesion was in the iliofemoral vein in 67, the veins of the calf in 49, the lower femoral and popliteal in 10, superficial varices in 8, the long saphenous in 3, and the subclavian in 1. In Table II a comparison of incidence of

TABLE II
POSTOPERATIVE THROMBOPHLEBITIS

	CONTROL GROUP: ANTICOAGULANTS NOT ADMINISTERED		DICUMAROL ADMINISTERED	
	NUMBER	PER CENT	NUMBER	PER CENT
Total cases	897	100	138	100
Subsequent episode of thrombophlebitis	95	10.6	4*	2.9
Subsequent fatal pulmonary embolism	51	5.7	0	0

*In two of these cases prothrombin was greater than 30 per cent when thrombophlebitis developed.

subsequent thrombophlebitis and subsequent fatal embolism is given with a control series, not treated with dicumarol, from a previous study.⁷ It is of interest that no instance of pulmonary embolism, fatal or non-fatal, occurred among any of the 138 patients treated with dicumarol. This is evidence that when thrombophlebitis is diagnosed clinically the thrombus which is present will almost certainly not detach and become an embolism. The danger from embolism in these cases occurs if a fresh thrombus suddenly propagates into a more proximal vein or if a fresh thrombus develops in a remote vein. If the development of such fresh thrombi is prevented, embolism can be prevented.

History of Thrombophlebitis or Embolism Previous to Operation.—Sixty-one patients with a history of thrombophlebitis or embolism previous to operation were given dicumarol beginning on the second post-operative day. In no case did embolism, fatal or nonfatal, develop. In two cases minor thrombophlebitis developed in superficial varices, but in both the prothrombin deficiency was inadequate (prothrombin content of plasma greater than 30 per cent of normal). No other instances of thrombosis developed.

Prophylaxis After Abdominal Hysterectomy.—Four hundred thirty-eight patients on whom abdominal hysterectomy had been performed and who had not had thrombophlebitis or embolism were given dicumarol for prophylactic purposes beginning on the second post-operative day. This group was selected because of the relatively high risk, compared with those on whom other operations are performed, of postoperative thrombophlebitis and embolism (4 per cent) and fatal embolism (0.7 per cent), as noted in a previous study.⁸ No embolisms developed in the cases in which dicumarol was given. In two cases thrombophlebitis of veins of the calf developed after the patients had left the hospital and after the prothrombin had returned to normal. No other thrombophlebitis developed.

Prophylaxis After Other Operations.—Cases in which prophylaxis was given after other operations comprised the remaining 183 patients. No thrombophlebitis or embolism developed in these cases but the group is too small to permit statistical comparison with similar cases in which treatment was not given.

RISK OF BLEEDING AMONG POSTOPERATIVE PATIENTS AFTER ADMINISTRATION OF DICUMAROL

The only hazard in the administration of dicumarol to postoperative patients is the risk of bleeding and we believe that it has been over-emphasized. In Table III the incidence of bleeding in the 1,000 cases

TABLE III
INCIDENCE OF BLEEDING AMONG PATIENTS TREATED POSTOPERATIVELY
WITH DICUMAROL

REASONS FOR DICUMAROL THERAPY	TOTAL NUMBER OF PATIENTS TREATED	MINOR BLEEDING		MAJOR BLEEDING	
		NUMBER	PER CENT OF TOTAL	NUMBER	PER CENT OF TOTAL
Postoperative pulmonary embolism	180	5	2.8	2	1.1
Postoperative thrombophlebitis	138	5	3.6	1	0.7
History of thrombosis or embolism at any time prior to immediate operation (prophylaxis)	61	1	1.6	1	1.6
Abdominal hysterectomy (prophylaxis)	438	20	4.6	12	2.7
Other operations (prophylaxis)	183	8	4.4	9	4.9
Total	1,000	39	3.9	25	2.5

is given. It will be noted that the incidence is very small among those patients who have already demonstrated a tendency to thrombosis. The total incidence of bleeding has been definitely smaller during the past two years than it was before since we have become more familiar with dosage and prevention and control of excessive and prolonged prothrombin deficiency. Minor bleeding, as mentioned in Table III, consisted of mild epistaxis, microscopic hematuria, and slight oozing from wounds, which may or may not have been caused by the prothrombin deficiency. Major bleeding, when it occurred, almost always came from surgical wounds, particularly the vaginal wound among patients on whom total abdominal hysterectomy had been performed. It was frequently controlled after one transfusion of blood or by intravenous injection of 64 mg. of menadione bisulfite. In a few cases repeated transfusions were necessary. One patient, who had a carcinoma of the third portion of the duodenum which entailed extensive resection with some trauma of the superior mesenteric vein and who was having continuous gastric drainage, was given dicumarol to prevent mesenteric thrombosis. However, only minimal prothrombin deficiency was produced, probably because of poor absorption of the drug. This patient had a massive, fatal gastrointestinal hemorrhage. It is unlikely that the prothrombin deficiency produced or even aggravated the bleeding in this case. No other cases of fatal bleeding occurred among the 1,000 patients treated. In almost all instances of major bleeding the prothrombin was less than 10 per cent of normal when the bleeding occurred. We feel that, if contraindications to the use of dicumarol are observed and there is careful individualization of dosage so that excessive prothrombin deficiency does not develop or is quickly controlled if it does develop, the danger of bleeding is very small.

CONTRAINDICATIONS

On the basis of our experiences we feel that the following conditions constitute definite contraindications to the use of dicumarol: (1) the presence of definite renal insufficiency; (2) the presence of definite hepatic insufficiency or hepatogenous jaundice, particularly if associated with prothrombin deficiency; (3) subacute bacterial endocarditis; (4) purpura of any type; (5) blood dyscrasia with tendency to bleed, and (6) recent operation on the brain or spinal cord. Dicumarol should be given cautiously to patients who have (1) ulcerative lesions, open wounds, or potentially bleeding surfaces; (2) vomiting due to gastric or intestinal obstruction; (3) continuous or repeated gastric or intestinal drainage, or (4) dietary or nutritional deficiency. If an operation is contemplated, ample time should be available for return of prothrombin to normal if dicumarol is administered before the operation. If emergency operation is necessary on a patient who has prothrombin deficiency owing to dicumarol, large doses of menadione bisulfite and blood transfusions should be given to combat the prothrombin deficiency before the operation is begun.

DOSAGE AND FREQUENCY OF ADMINISTRATION

The purpose of dicumarol therapy is to produce a certain degree of prothrombin insufficiency. As with many other potent drugs, there is considerable variation in sensitivity to the drug among different patients. Absorption of the drug from the intestinal tract probably varies in different cases and there is some evidence that the effect may vary with the weight of the patient. The presence of fever, toxemia, and impaired nutrition also may influence the effect but there are still other unexplained differences in sensitivity. For these reasons it is necessary to individualize carefully the rate of administration of the drug for each patient.

We wish to emphasize again that dicumarol should not be used unless daily and consistently comparable prothrombin time tests are done, since without these it is impossible to be certain whether insufficient, adequate, or excessive and possibly dangerous effects have been produced. We believe that only the Quick prothrombin time test should be used for these determinations. Because of the importance of this test, some details regarding the technique and possible errors in comparative determinations should be mentioned.

The actual performance of the test is not difficult. Whole blood drawn from a vein is added to tenth-molar sodium oxalate in the proportion of 9:1. After a short period of centrifugation, 0.1 c.c. of plasma is placed in a small test tube and 0.1 c.c. of thromboplastin is added to the plasma. The tube with its contents is held in a constant temperature bath of 37.5° C. After a few moments 0.1 c.c. of fortieth-molar calcium chloride is added and at the exact instant when it is added, a stop clock (preferably operated with a foot pedal) is started. The tube is carefully agitated and then tilted at intervals to determine the moment at which a semisolid clot is formed; this is the end point and the clock is stopped. It is a sharp end point and can be duplicated by any technician who has had reasonable experience.

It is obvious from the description of the method that if there were no variables except prothrombin, the test could be considered a simple one. Unfortunately, the thromboplastin is distinctly a variable under certain conditions and the clotting time is dependent to a great extent on the activity of the thromboplastic substance. At the Mayo Clinic the thromboplastin which is used in the test is prepared from dried rabbit brain according to Quick's original method,^{9, 10} that is, without previous extraction with acetone. We obtain a normal prothrombin time with this thromboplastin of seventeen to nineteen seconds. Some workers, however, follow Quick's modification of his earlier method.¹¹ In this modification he extracted the brain with acetone previous to the drying process. With this substance Quick obtained a normal prothrombin time of twelve to thirteen seconds and, with this, more active preparation times for various levels of prothrombin deficiency are all correspondingly

lower but by no means exactly six seconds lower for each level. Thromboplastins which give still different normal prothrombin times and therefore different and incomparable times for various levels of prothrombin deficiency have been used by other workers. Variations in results also may occur because two batches of thromboplastin which are made up in the same way and which give identical prothrombin times for normal plasma may not give identical times for a plasma with a moderate or marked prothrombin deficiency. As a result of our clinical experiences with dicumarol we found that prothrombin times of twenty-seven seconds, thirty-five seconds, and sixty seconds were indicative of certain important levels of prothrombin deficiency. However, such figures are meaningless to another worker using a different thromboplastin of different activity.

If normal plasma is diluted with prothrombin-free plasma so that 90 per cent, 80 per cent, and so forth down to 10 per cent solutions of normal plasma are obtained and prothrombin time tests are done on these various diluted samples, a curve can be plotted which will indicate prothrombin times for various percentage levels of prothrombin deficiency. An almost identical curve can be obtained if the dilution is made with physiologic solution of sodium chloride, except that it is more difficult to read end points in the higher dilutions. It is noteworthy that this curve is not a straight line. For example, the first few seconds' increase in the prothrombin time indicates a great decrease in the prothrombin percentage of normal but when the prothrombin deficiency becomes marked, many seconds' increase may mean a difference of only a few per cent in the concentration of prothrombin.

By plotting a dilution curve as indicated in the previous paragraph, any worker using a thromboplastin of unknown potency can determine a set of prothrombin times for that thromboplastic substance which indicate various percentages of prothrombin deficiency and if certain prothrombin percentages are considered important levels, he can easily determine their equivalents in prothrombin times.

Because of the variability of potency of thromboplastic substances, even when prepared by the same method, and because of the importance of having consistently comparable results from day to day when the test is used as a guide to dicumarol therapy, each new batch of thromboplastic substance should be checked against the one in use by one of two methods. Either only a new thromboplastin should be selected which gives the same results as the old, both with normal plasma and with a number of prothrombin deficient plasmas which are deficient to varying degrees, or a new dilution curve should be plotted for each new batch of thromboplastin. It may be advisable to check results on the same batch of thromboplastin if it is more than twenty-four hours old. As will be shown later, the important prothrombin times for patients receiving dicumarol are those for 10 per cent, 20 per cent, 30 per cent, and 100 per cent normal plasma. Determinations on other dilutions are

actually not necessary. It may be preferable from the standpoint of the clinician or surgeon who is supervising the administration of dicumarol that the reports be given in percentages of normal prothrombin rather than in seconds....

Our experience in the 1,000 cases in which dicumarol was used has been that with the thromboplastic substance which we have used, thrombosis or embolism almost certainly did not develop if the prothrombin time was greater than twenty-seven seconds, the time which corresponded to that of 30 per cent normal plasma, and that definite bleeding did not occur if the prothrombin time was less than sixty seconds, the time which corresponded to that of 10 per cent normal plasma. We have adopted arbitrarily thirty-five seconds, the time for 20 per cent normal plasma, as the key point in deciding about the dosage.

Dicumarol is effective when administered orally. A satisfactory preparation for parenteral administration has not been developed. We have endeavored to simplify the plan of administration as far as possible in order to keep the prothrombin level between 10 and 30 per cent of normal for each individual patient and we recommend the following plan of dosage: The entire amount of the drug for each day is given in a single dose. The first day 300 mg. are given and 200 mg. are given the second day. Two hundred milligrams are given on each succeeding day that the prothrombin is greater than 20 per cent of normal. If it is less than 20 per cent of normal, no dicumarol is given on that day. Exceptions are occasionally made as follows: If the prothrombin is dropping rapidly, but is still slightly greater than 20 per cent, no drug is given. If it is rising rapidly, but has not quite reached 20 per cent, a dose is given on that day. In the occasional patient who is found to be quite hypersensitive to the drug, it may be advisable to reduce some or all of the doses to 100 mg. In the occasional case of resistance, it may be advisable to increase them to 300 mg. For patients who have never had thrombosis or embolism and to whom the drug is given purely for prophylaxis, it may be advisable to omit the dose on the second day in order to be sure that the patient is not hypersensitive.

It must be re-emphasized that definite prothrombin deficiency does not develop immediately after the drug has been given. Effective levels are not reached for twenty-four to forty-eight hours and sometimes for a considerably longer time. If a rapid anticoagulant effect is desired, for example in a case of a large pulmonary embolism, administration of heparin and dicumarol should be started simultaneously. The prothrombin time may be used as a guide to the dicumarol effect alone if the blood is drawn for the test from three to four hours after an injection of heparin is given. Administration of heparin should be stopped as soon as the prothrombin has dropped to 20 per cent of normal. In dealing with patients who have had thrombophlebitis or a small pulmonary embolism we have rarely used heparin in addition to dicumarol and have almost never encountered a second episode of thrombosis or embolism during the one to three days which have elapsed

between the beginning of administration of dicumarol and the development of adequate prothrombin deficiency. Also it must be re-emphasized that the prothrombin deficiency may continue for from two to ten days after the last dose of dicumarol has been given. Daily prothrombin time tests should be continued until near normal levels of prothrombin have been reached.

We have maintained the prothrombin deficiency produced by dicumarol at levels between 10 and 30 per cent of normal for as long as three months among postoperative patients without untoward effect, without evidence of other impairment of hepatic function as measured by the ordinary tests, and with prompt return of prothrombin to normal within a few days after the administration of the drug was discontinued.

The prothrombin deficiency should be maintained until several days, preferably a week, after the patient has become ambulatory. The thrombosing tendency has almost certainly disappeared by that time. However, it must be emphasized that when the prothrombin has returned to normal there is no further protection against thrombosis.

CONTROL OF BLEEDING AND EXCESSIVE PROTHROMBIN DEFICIENCY

If, because of hemorrhage or abnormally high prothrombin times, it is advisable to lower the prothrombin time, this usually can be accomplished by the transfusion of 500 c.c. of fresh citrated blood (bank blood may be ineffective). It may be necessary to transfuse blood several times over a period of two or three days, since there is a tendency for the prothrombin time to increase again after two to six hours have elapsed. The effect of blood transfused for such a purpose apparently is due simply to a replacement of prothrombin, and blood which has been stored for more than twenty-four hours in the icebox may have lost much of its prothrombin.

In the original studies on dicumarol it was found that the administration of what were considered to be therapeutic doses of synthetic vitamin K did not inhibit the action of dicumarol or affect the hypoprothrombinemia which had been produced by dicumarol. However, it is now known that these doses were much too small. Overman, Stahlmann, and Link¹² have pointed out that vitamin K inhibits the effect of dicumarol if given in large doses to rabbits. Shapiro, Redish, and Campbell¹³ found that large amounts of synthetic vitamin K, given by mouth and intramuscularly to human beings, prevented the prolongation of prothrombin time following administration of dicumarol. By the intravenous administration of large doses of a special preparation of vitamin K₁ oxide, Davidson and MacDonald¹⁴ were able in three of four cases to reverse to normal the prolonged prothrombin time induced by dicumarol. Lehmann¹⁵ reported that the use of large doses of methylnaphthoquinone dihydrosulfate given orally with blood transfusions resulted in cessation of hemorrhage which had followed administration of dicumarol.

In the course of this study menadione bisulfite,⁹ usually in a single dose of 34 mg., was administered intravenously to thirty-seven patients among whom an excessive deficiency of prothrombin had developed after administration of dicumarol. All but two patients responded satisfactorily to administration of menadione bisulfite. In thirty-two cases a marked and relatively rapid lowering of prothrombin time occurred, and in the other three, although the response was not great, the prothrombin time fell to within safe limits. No toxic or untoward reactions followed administration of menadione bisulfite.¹⁶

Bleeding which had occurred in three cases after administration of dicumarol, ceased after administration of menadione bisulfite in two cases and after administration of menadione bisulfite and a blood transfusion in the third case.

Patients may be encountered who are sensitive to dicumarol and whose prothrombin may fall to less than 10 per cent of normal after the first one or two doses or after subsequent doses. Ninety-three such patients (27 per cent) were encountered in a consecutive series of 340 who received dicumarol. Most of these were patients who had not had thrombosis or embolism. It is in this group that bleeding may occur, although it actually occurred in only three of these series of ninety-three. The safest procedure is to give a large dose (60 to 64 mg.) of menadione bisulfite intravenously to all patients whose prothrombin falls below 10 per cent of normal after administration of dicumarol and to use smaller doses of dicumarol thereafter. If bleeding of any serious or alarming degree occurs among patients who are receiving dicumarol, a large dose of menadione bisulfite should be given intravenously and a transfusion of fresh citrated blood should be given. Subsequent transfusions of blood should be given once or twice daily until the bleeding stops. The actual risk of bleeding is small among postoperative patients if the method of dosage and control mentioned previously is followed. It is particularly small among patients who have had some thrombotic or embolic episode (Table III).

COMMENT

When properly used, anticoagulant therapy with dicumarol and occasionally with heparin also for the first few days appears to us to be the most satisfactory method to date for the prevention of fatal postoperative pulmonary embolism. The risk of bleeding is minimal and if bleeding occurs it can be satisfactorily controlled. However, the prothrombin must be kept between 10 and 30 per cent of normal if the treatment is to be effective and safe. As opposed to ligation of one or both femoral or common iliac veins, anticoagulant therapy prevents venous thrombosis throughout the entire body. It is relatively simple,

⁹The preparation of menadione bisulfite was "hykinone" supplied through the courtesy of the Abbott Laboratories, North Chicago, Ill. Sixty-two and five-tenths per cent of hykinone is menadione (2-methyl-naphthoquinone).

does not involve further surgical procedures, and does not produce complete obstruction of veins containing thrombi which might undergo partial or complete involution. Therefore, it does not increase the hazard of chronic venous insufficiency of one or both legs with its disabling late complications.

Anticoagulant therapy seems to us particularly the preventive method of choice in cases of nonfatal postoperative pulmonary embolism or infarction in which the source of the embolus is not detectable clinically, in cases in which thrombosis or embolism has occurred prior to operation, and in those in which thrombosis or embolism has not occurred but in which it is thought that there is increased risk of these complications. Even in cases in which known venous thrombosis is present, anticoagulant therapy will prevent embolism because embolism develops only if a fresh thrombus develops. The old clots remain attached to the wall of the vein.

SUMMARY

Dicumarol has been given to 1,000 patients for the purpose of preventing postoperative venous thrombosis, pulmonary embolism, and thrombophlebitis. We have found it effective in preventing these complications in cases in which there has been nonfatal pulmonary embolism, thrombophlebitis or a history of previous thrombosis or embolism, and when the drug has been given prophylactically when no thrombosis or embolism has occurred. There is a small risk of bleeding. This can be further minimized by proper administration of the drug and rapid control of excessive prothrombin deficiency. Dicumarol should not be given unless daily and consistently comparable Quick prothrombin time tests are done. Consistently comparable prothrombin time tests depend on the use of thromboplastins of constant potency or on the checking of each new batch of thromboplastin with various dilutions of normal plasma. During the administration of dicumarol the prothrombin should be kept between 10 and 30 per cent of normal. Excessive prothrombin deficiency produced by dicumarol can almost always be controlled by the intravenous administration of large doses (60 to 64 mg.) of menadi-one bisulfite (synthetic vitamin K). If bleeding occurs as the result of excessive prothrombin deficiency, it can be controlled by transfusions of freshly drawn citrated blood and intravenous administration of large doses of menadi-one bisulfite.

REFERENCES

1. Campbell, H. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease; IV. The Isolation and Crystallization of the Hemorrhagic Agent, *J. Biol. Chem.* 138: 21-33, 1941.
2. Stahmann, M. A., Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease; V. Identification and Synthesis of the Hemorrhagic Agent, *J. Biol. Chem.* 138: 513-527, 1941.
3. Butt, H. R., Allen, E. V., and Bollman, J. L.: A Preparation From Spoiled Sweet Clover [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood: Preliminary Report of Experimental and Clinical Studies, *Proc. Staff Meet., Mayo Clin.* 16: 388-395, 1941.

4. Bingham, J. B., Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3'-Methylenebis-(4-Hydroxycoumarin); I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, *Am. J. M. Sc.* 202: 563-578, 1941.
5. Allen, E. V., Barker, N. W., and Waugh, J. M.: A Preparation From Spoiled Sweet Clover [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood; a Clinical Study, *J. A. M. A.* 120: 1009-1015, 1942.
6. Barker, N. W.: The Use of Dicumarol in Surgery, *Minnesota Med.* 27: 102-106, 1944.
7. Barker, N. W., Nygaard, K. K., Walters, Waltman, and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism; III. Time of Occurrence During the Postoperative Period, *Proc. Staff Meet., Mayo Clin.* 16: 17-21, 1941.
8. Barker, N. W., Nygaard, K. K., Walters, Waltman, and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism; I. Incidence in Various Types of Operations, *Proc. Staff Meet., Mayo Clin.* 15: 769-773, 1940.
9. Quick, A. J., Stanley-Brown, Margaret, and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and in Jaundice, *Am. J. M. Sc.* 190: 501-511, 1935.
10. Magath, T. B.: Technic of the Prothrombin Time Determination, *Am. J. Clin. Path. (Tech. Suppl.)* 3: 187-189, 1939.
11. Quick, A. J.: The Nature of the Bleeding in Jaundice, *J. A. M. A.* 110: 1658-1662, 1938.
12. Overman, R. S., Stahlmann, M. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease; VIII. The Effect of 2-Methyl-1, 4-Naphthoquinone and l-Absorbic Acid Upon the Action of 3,3'-Methylenebis-(4-Hydroxycoumarin) on the Prothrombin Time of Rabbits, *J. Biol. Chem.* 145: 155-162, 1942.
13. Shapiro, Shepard, Redish, M. H., and Campbell, H. A.: Prothrombin Studies; III. Effect of Vitamin K Upon Hypoprothrombinemia Induced by Dicumarol in Man, *Proc. Soc. Exper. Biol. & Med.* 52: 12-15, 1943.
14. Davidson, C. S., and MacDonald, Harriet: The Effect of Vitamin K, Oxide on Hypoprothrombinemia Induced by Dicoumarol, *New England J. Med.* 229: 353-355, 1943.
15. Lehmann, Jürgen: Thrombosis; Treatment and Prevention With Methylene-Bis-(Hydroxycoumarin), *Lancet* 1: 611-613, 1943.
16. Cromer, H. E., Jr., and Barker, N. W.: The Effect of Large Doses of Menadi-one Bisulfite (Synthetic Vitamin K) on Excessive Hypoprothrombinemia Induced by Dicumarol, *Proc. Staff Meet., Mayo Clin.* 19: 217-223, 1944.

SURGERY OF DEEP VENOUS THROMBOSIS OF THE LOWER EXTREMITY

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ONCE thrombosis of the peripheral veins has developed, the objects of treatment are to limit propagation of the thrombus, to prevent pulmonary embolism, and to correct the local impairment of circulation. The method selected for obtaining these objects depends upon the type of thrombosis and the presence or absence of pulmonary embolism. At the present state of our knowledge, the only practical method in the great majority of cases is by surgical ligation of the appropriate vein above the level of thrombosis. Our purpose in this report is to present the experience with ninety-eight ligations of the major veins of the lower extremity for the treatment of deep vein thrombosis in eighty-four consecutive cases.

CLASSIFICATION

There are too many gaps in the fundamental knowledge of the etiology of venous thrombosis to allow a comprehensive classification. In general, however, cases involving the lower limb can be divided into two main groups: Acute thrombophlebitis and simple thrombosis (phlebothrombosis).

In acute thrombophlebitis, there is antecedent or concomitant inflammation of the vein wall. The clot forms on the intima, is firmly fixed, grows by accretion, and tends rapidly to fill the lumen completely along the involved segment. Acute iliofemoral thrombophlebitis is a typical example. The symptoms of this condition arise partly from inflammation and occlusion of a major vein and partly from reflex arterial spasm.^{1,2} Release of the vasospasm by means of lumbar sympathetic block (procaine) promptly relieves the symptoms of ischemia and limits extension of the thrombosis. With this form of treatment, recovery from the acute phase is usually complete within seven to ten days, and the ultimate results are most gratifying. Occasionally, pulmonary embolism follows detachment of a fresh thrombus which has formed above the inflamed segment of vein. In this event, ligation of the vein above the thrombus is the only safe method for preventing recurrent embolism.

Simple thrombosis (phlebothrombosis) most commonly begins in the small deep veins of the foot or leg. It differs from acute thrombophlebitis mainly by the absence of important inflammatory reaction in the early phase, by its tendency to propagate rapidly, and by the ease with which it becomes dislodged to cause pulmonary embolism.

Between these two distinct types of venous thrombosis are many intermediate forms, which do not fall readily into any scheme of classification. Actually, most of the cases in this intermediate group undoubtedly begin as phlebothrombosis. Later a secondary inflammatory reaction may develop in and around the vein wall, so that the picture of acute thrombophlebitis is simulated. However, even at this stage the clot may not be firmly fixed to the endothelium and dislodgment remains a potential hazard. The existence of this intermediate group, plus the fact that embolism is occasionally seen in cases of typical acute thrombophlebitis, detracts greatly from the utility of the present system of classification. The eighty-four cases with which this presentation deals were all characterized by thrombosis of the type which begins in the lower leg and which shows a strong tendency to propagate. No attempt will be made to divide them into groups.

ETIOLOGY

The exact causes of intravascular clotting are still a mystery. Since this paper entails a purely clinical approach to one phase of venous thrombosis, it seems permissible to omit from discussion much that has been written about the etiology of the condition. From a clinical viewpoint the etiology of peripheral venous thrombosis is mainly a consideration of predisposing causes. In the eighty-four cases which are the basis of this report, some of the more important predisposing causes are shown in Fig. 1 and Table I.

Sex.—Of the eighty-four cases, fifty-five of the patients were men and twenty-nine were women. The incidence of the type of venous thrombosis for which surgical treatment is indicated is therefore considerably

TABLE I

PREDISPOSING DISEASE OR CONDITION AND INCIDENCE OF PULMONARY EMBOLISM IN 84 CASES OF DEEP VENOUS THROMBOSIS OF THE LOWER EXTREMITY

DISEASE OR CONDITION	NUMBER OF CASES	CASES WITH PULMONARY EMBOLISM
None (spontaneous)	20	11
Postoperative	20	10
Heart failure	12	7
Pulmonary tuberculosis	8	1
Pneumonia	5	3
Disease or injury of lower extremity	12	3
Fracture	4	
Cellulitis	3	
Gangrene	2	
Sprain	1	
Injected varicose vein	1	
Arthritis of knee	1	
Pregnancy	2	1
Severe burns	1	0
Prostatism	1	1
Meningitis	1	1
Cachexia	1	0
Influenza	1	1
Totals	84	39

higher in men than in women. This finding is in agreement with other reports.^{3, 4} It is contrary to the experience with acute thrombophlebitis in which the ratio of women to men is reported as 3:2.⁵

Age.—Any type of peripheral venous thrombosis is very rare in the first two decades of life. The type with which we are dealing is not common until the fourth decade, and the majority of cases are after the fourth decade. About 70 per cent of the eighty-four cases involved patients over 40 years of age. This is in fairly close agreement with the findings of Allen, Linton, and Donaldson³ who reported that 81 per cent of 202 patients with thrombo-embolic disease were over 40.

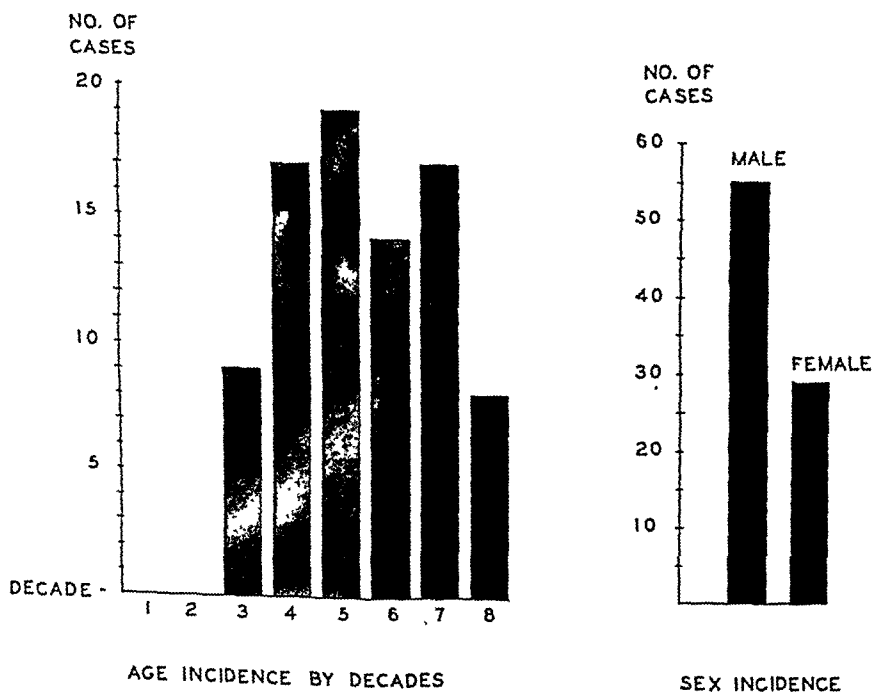


Fig. 1.—Predisposing factors in etiology of eighty-four cases of deep vein thrombosis.

Predisposing Diseases or Conditions.—The idea has been prevalent for years that thrombosis of the deep veins of the lower extremity is most common following pregnancy and abdominal operations. Hunter and his co-workers⁶ demonstrated at necropsy, however, that in middle-aged and elderly patients the incidence of thrombosis of the deep veins of the leg is about equal in medical and surgical patients. Furthermore, Hampton and Castleman⁷ found that in 370 autopsy cases of pulmonary embolism, 60 per cent were in medical cases and 40 per cent in surgical cases.

In the eighty-four cases of this series (Table I), only twenty were post-operative patients. Fifteen of the operations were on the abdomen, three were orthopedic operations, one was the removal of a brain tumor, and one was a lumbar sympathectomy for frostbite of the foot. This last

case is of particular interest because the thrombosis developed about eight days after a successful right lumbar sympathectomy. The thrombus was located in the lower part of the right femoral vein, as demonstrated by means of a venogram. Pulmonary embolism resulted in this case before the femoral vein was ligated.

There were also twenty cases in which thrombosis of the deep veins of the lower limb occurred spontaneously in individuals who were pursuing their usual routine of life. In four of these cases, thrombosis started in varicose veins and extended into the deep veins. In the remaining sixteen cases there was no history or evidence of previous disease of the veins, and the thrombus originated in the tibial veins. There was considerable variation in the types of activity in which the patients were engaged at the time of onset. Some of the activities included prolonged sitting in a cramped position, undressing in a Pullman berth, walking uphill while carrying a heavy load on the back, lifting a heavy weight, hiking to the point of fatigue, and prolonged standing at work. It is possible that there is one factor common to many of these cases, namely, distention and delayed emptying of the veins.

There were twelve cases of thrombosis in patients with heart failure. There was only one patient in this group less than 40 years old. The average age was 54 years. All of these patients had severe heart failure at the time of development of venous thrombosis. The factors which predispose to this complication in cardiac patients include venous stasis,⁸ prolonged bed rest and free use of sedatives in treatment of the disease,⁹ and possibly digitalization.¹⁰ It is a curious fact that all of these factors prevail in children with heart failure, but thrombo-embolic phenomena are quite rare.¹¹

Twelve of the eighty-four patients had thrombosis secondary to disease or injury of the lower extremity. Six of these resulted directly from injury to the bones or soft tissues of the extremity. Three followed cellulitis of the foot and leg. Two resulted from gangrene of the toes. The remaining case was one of severe arthritis of the knee. In all of these cases, with the possible exception of the last-mentioned, it is easy to conceive that the veins of the leg may have been directly involved by the disease or injury. In gangrene due to vascular diseases of the lower extremity, thrombosis of the deep veins is quite common. This is usually attributed to the slowing of the venous blood flow because of the diminished volume of arterial circulation. The prevalence of femoral vein thrombosis following thigh amputation has been emphasized by Veal,¹² who demonstrated a considerable reduction in the incidence of pulmonary embolism by high ligation of the femoral vein before amputation.

There were eight cases in patients with pulmonary tuberculosis who were on a regimen of strict bed rest. This group is of particular interest to us because of the slight attention that has been given to the vascular system in patients with this disease.

In the five cases of pneumonia, the patients were all seriously ill at the time that venous thrombosis developed. The remaining cases need no special comment.

It is obvious that in all of the eighty-four cases except the ones classed as "spontaneous," the conditions which predisposed to venous thrombosis were mainly ones in which prolonged rest in bed may have been the principal factor in the pathogenesis of the disease. We have omitted from analysis certain other conditions which are known^{5, 8} to predispose to venous thrombosis, including obesity, infection, anemia, and malignant neoplasm.

SYMPTOMATOLOGY

In the eighty-four cases the symptom which first drew attention to the existence of thrombosis of the deep veins of the lower extremity was pain in the leg in sixty-one cases, evidence of pulmonary embolism in sixteen cases, and swelling of the leg in seven cases. The incidence of additional signs of the thrombosis is shown in Table II.

There was great variation in the type and degree of pain in the leg in the sixty-one cases in which it was a prominent symptom. Almost always the pain was located in the calf. In our experience, pain in the foot is a rare presenting symptom. In the patients who were well and active at the time of onset, the pain usually began suddenly and was sharp, persistent, and well localized in the calf. In bedridden patients the pain was variably described as constricting, aching, boring, or burning. Often the discomfort was intermittent, with or without reference to movement of the leg. On occasion, the pain was noticed for the first time when a patient who had been kept in bed was allowed to stand. In general, the pain was less severe and less well localized in the case of patients in bed. In many instances the patient noted that the pain extended in time from the calf into the popliteal region or thigh. The pain was almost never so severe as is seen in cases of acute iliofemoral thrombophlebitis.

The manifestations of pulmonary embolism as a presenting symptom will be discussed separately in a section to follow.

TABLE II
INCIDENCE OF VARIOUS SIGNS IN 84 CASES OF DEEP VENOUS THROMBOSIS OF THE LOWER EXTREMITY

SIGN	PRESENT		ABSENT	NOT RECORDED
	SIGNIFICANT*	NOT SIGNIFICANT		
Edema	72 (90%)	0	8	4
Calf tenderness	78 (96%)	0	3	3
Homans' sign	68 (92%)	0	6	10
Fever	12 (14%)	41	31	0
Tachycardia	18 (21%)	49	17	0

*The percentage figures in this column were obtained after excluding cases in which no record was made of the sign.

There were only seven cases in which edema of the foot or foot and leg was the first evidence noted of venous thrombosis. These were all

patients who were bedridden. In some of them the edema was erroneously ascribed at first to some other cause. We mention this fact only to emphasize the importance for the safety of the patient of remembering the possibility of venous thrombosis in any case of edema of the lower extremity. This is probably just as true whether or not there seems to be another obvious cause for the edema, such as heart failure or malnutrition. Although edema was the least common presenting symptom in the eighty-four cases, it was present at some time before surgical ligation of the affected veins in seventy-two cases. In four cases no record was made as to whether or not there was edema. We have included as instances of edema those cases in which the only evidence of its presence was enlargement of the calf, as detected by comparative measurements of both legs.

The most common sign of all was tenderness in some portion of the calf. This was elicited in seventy-eight of the eighty-one patients who were examined for it. A good deal of care is necessary in testing for calf tenderness. The patient's leg should be slightly flexed, so that the muscles are relaxed. Finger-point palpation should be made along the course of the deep veins, beginning at the plantar surface of the foot. Often the area of tenderness is quite small and well localized, but this is all the more significant.

Forcible dorsiflexion of the foot with the leg extended caused pain in the calf or popliteal area (Homans' sign) in sixty-eight cases. The results of this test were not recorded in ten cases. There were only six cases in which the test was negative. Allen, Linton, and Donaldson³ reported this sign to be present in only 42 per cent of the cases in which the test was applied. Our experience, therefore, supports the contention of the author¹³ who described the sign, that it may be expected to be found in a very high percentage of cases of tibial vein thrombosis. However, it should not be thought to be pathognomonic. It may be positive in a variety of other conditions, including peripheral neuritis, paralysis with foot drop, poliomyelitis, contusions without deep vein thrombosis, and cellulitis of the leg.

Fever and tachycardia, which are almost always present in acute iliofemoral thrombophlebitis, are not very helpful diagnostic signs in the type of venous thrombosis with which we are here concerned. These signs are usually lacking in the early stages of the thrombotic process, unless some other cause for fever and tachycardia is present. In the eighty-four cases, fifty-three patients had fever at the time a diagnosis of venous thrombosis was made. However, in all but twelve of these patients the fever could be accounted for by the primary disease from which the patient was suffering or by pulmonary embolism. Sixty-seven patients had tachycardia, but on the same basis of analysis it was significant of venous thrombosis in only eighteen.

Venograms were made in only twenty-seven of the eighty-four cases. We have not used this type of study routinely nor do we advocate this.

The interpretation of venograms requires considerable experience with variations in normal venous patterns. This fact, plus the knowledge that a diagnosis of venous thrombosis can usually be made, by means of simpler methods, limits the usefulness of the procedure. However, we have found that the venogram is an important aid in doubtful cases. In our experience a normal venogram usually excludes the diagnosis of thrombosis in the region studied.

PULMONARY EMBOLISM

In sixteen of this group of eighty-four cases, pulmonary embolism was the initial symptom that directed attention to the venous thrombosis, and in twenty-three additional cases pulmonary embolism preceded surgical ligation. This incidence is somewhat higher than was reported by Welch and Faxon,¹⁴ who state that approximately one out of every three patients with deep phlebitis may be expected to have pulmonary embolism. However, it must be remembered that our figures deal only with cases in which ligation of a vein was performed and do not include a statistical study of pulmonary embolism in all cases of venous thrombosis.

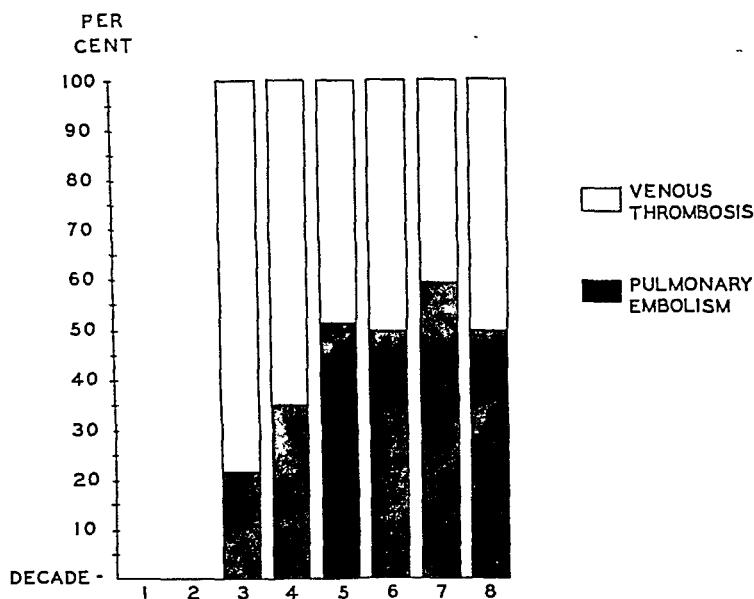


Fig. 2.—Incidence of pulmonary embolism by decades in eighty-four cases of deep vein thrombosis of lower limb.

Fig. 2 shows the incidence of pulmonary embolism by age in our cases. Of the patients in the third decade, 22 per cent had pulmonary embolism, and in the fourth decade, 35 per cent. Above the age of 40, slightly more than 50 per cent of the patients had pulmonary embolism, and there was remarkably little variation in the frequency of the complication in the different decades.

It has been our experience that cases of venous thrombosis are referred to the vascular surgeon in many stages of the thrombotic process. In

some cases the process is in an early phase, in others the disease has been present for weeks or even months before surgery is considered. The symptomatology varies correspondingly. Of prime importance in all cases is the prevention of pulmonary embolism. The surgeon, therefore, must answer the following question in each case: Is pulmonary embolism a potential danger, or has this case reached a "safe" period with respect to pulmonary embolism? We have already given the answer to the first part of this question. In all cases of venous thrombosis there is at some time danger of embolism. The latter part of the question is answered partially by the figures in Table III. This table shows the frequency of embolism in relation to the known duration of the thrombotic process. The sixteen cases in which pulmonary embolism occurred before the venous thrombosis was discovered are excluded from the table. The figures show that there is no "safe" period for all cases in the chronology of the disease up to four months.

In our discussion of the classification of deep venous thrombosis we have pointed out that the clinical picture in any case is not a perfectly reliable means for deciding about the likelihood of pulmonary embolism. Simple thrombosis of the deep veins of the calf, by propagation of the thrombus and secondary inflammatory reaction around the vein, may simulate acute iliofemoral thrombophlebitis, including massive edema. We have repeatedly observed at operation in such cases that the thrombus in the iliac veins does not necessarily become fixed to the intima for days or even weeks. We have also found that repeated

TABLE III

RELATION OF FREQUENCY OF PULMONARY EMBOLISM TO KNOWN DURATION OF VENOUS THROMBOSIS IN 68 CASES IN WHICH PULMONARY EMBOLISM WAS NOT THE FIRST MANIFESTATION

DURATION OF THROMBOSIS	TOTAL CASES	PATIENTS WITH EMBOLISM
Uncertain	5	3
1 Day	6	0
2 Days	6	1
3 Days	10	1
4 Days	4	0
5 Days	5	3
6 Days	1	0
7 Days	5	2
1 to 2 Weeks	9	2
2 to 3 Weeks	8	5
3 to 4 Weeks	4	3
5 to 6 Weeks	2	0
2 Months	3	2
4 Months	1	1

pulmonary embolism is common in these cases. Usually the emboli are small and arise from fresh clot engrafted on the older, organizing thrombus. We have recently observed at necropsy three examples of death from massive pulmonary embolism in cases of acute iliofemoral thrombophlebitis (phlegmasia alba dolens). In each instance the em-

bolus originated from a fresh thrombus engrafted on the older clot in the iliac vein. The vessels of the opposite extremity were entirely normal. We mention these points in order to temper a recent statement by Homans¹⁵ to the effect that if pulmonary embolism occurs in cases of phlegmasia alba dolens, "one can be reasonably certain that it comes, not from the vein of the swollen limb but from the other, or innocent appearing leg." We quite agree, however, that when one lower extremity is the seat of venous thrombosis, the innocent-appearing limb should always be viewed with suspicion. This will be borne out in the discussion to follow on embolism after venous ligation.

One other question which deserves clarification concerns whether the circumstances under which venous thrombosis develops have any direct bearing on the frequency of pulmonary embolism. The incidence of this complication in the various predisposing diseases or conditions in our eighty-four cases is shown in Table I. We wish to emphasize particularly that the incidence was eleven out of twenty in the cases in which venous thrombosis occurred in active, apparently healthy individuals. This fact certainly demonstrates that a patient need not be bedridden to develop the type of venous thrombosis which leads to pulmonary embolism.

Pulmonary embolism which occurs after ligation of a major vein may originate from one of several sources. The most frequent source is undoubtedly from thrombosis in veins of the opposite lower extremity. It also may originate from a thrombus which forms in the ligated vein above the level of ligation, from veins in other parts of the body, or from thrombi in the right side of the heart. In nine of our eighty-four cases, the patient had pulmonary embolism after ligation of one or more veins. In each of these nine cases there had already been one or more episodes of pulmonary embolism before ligation. In five instances the embolus arose from the opposite, unoperated extremity, and in three the embolism was fatal. In four cases the embolus originated from a fresh thrombus above the point of ligation. In all of these the femoral vein had been ligated distal to the saphenous.

In forty-five cases the appropriate vein or veins were ligated as soon as venous thrombosis was recognized, and in none of these did pulmonary embolism develop.

OPERATIONS

The sites of ligation of veins in ninety-eight consecutive operations in eighty-four cases are shown in Table IV.⁴ It is interesting to note that the veins of the right leg alone were involved in thirty-five cases, the left leg alone in thirty-three cases, and both legs in sixteen cases. Thus, the frequency of thrombosis was about equal in the right and left lower

⁴In this paper we have used the term "ligation" loosely. Actually, in almost all cases, the procedure has consisted of opening the vein for inspection, ligating above and below the opening, and dividing the vein between these ligatures.

extremity. This experience is somewhat at variance with the statistical report of Barker and his co-workers¹⁶ to the effect that thrombophlebitis is about twice as common in the left lower extremity as in the right. Of great importance is the fact that in our patients about one-fifth had venous thrombosis in both lower extremities.

TABLE IV

SITES OF LIGATION FOR TREATMENT OF 84 CASES OF THROMBOSIS OF DEEP VEINS OF LOWER EXTREMITY

SITES OF LIGATION	NUMBER OF CASES
Right femoral	20
Right femoral (thrombectomy)	1
Left femoral	19
Left femoral (thrombectomy)	3
Right external iliac	4
Left external iliac	1
Right common iliac	7
Right common iliac (thrombectomy)	3
Left common iliac	7
Left common iliac (thrombectomy)	3
Inferior vena cava	2
Multiple operations	
Both femorals (simultaneous)	6
Right common iliac and left femoral (simultaneous)	1
Both common iliacs (separate)	3
Left common iliac (thrombectomy) and inferior vena cava (thrombectomy)	2
Left external iliac and inferior vena cava	1
Right femoral and inferior vena cava	1
Total cases	84
	(Total ligations, 98)

As yet the operative treatment of venous thrombosis is not completely standardized. In all reports there is considerable variation of opinion as to the level at which ligation should be done. We have attempted to follow one rule: Ligate the affected vein above the level of the thrombus in a normal segment of vein just distal to a main tributary. By this means the entire pathologic process is trapped below the point of ligation. The main tributary assures an adequate flow of blood to diminish the chance of development of a fresh thrombus. This also excludes a blind end of vein in which a thrombus may form. There is great danger of recurrent thrombosis when ligation is performed through a diseased segment of vein, although the clot may have been removed or may not have extended to this level. We have had four cases of recurrent pulmonary embolism following ligation of the femoral vein through a diseased segment. We have had other cases in which a thrombus formed above the point of ligation through a diseased segment and extended into the inferior vena cava, making a secondary and more hazardous operation necessary.

In cases in which, on exploration, a clot is found at the level of operation, the course to be followed depends upon the age of the thrombus and the condition of the vein wall. A fresh clot is blue, elastic, resilient,

and unattached to the intima. This type of clot can be removed safely, providing that the vein wall shows no sign of inflammation. When the vein wall is definitely inflamed, regardless of the appearance of the clot, it is safer to go higher and ligate the vein where it appears normal. When the clot is old and organizing, it is brownish and friable. Thrombectomy is then dangerous because of the likelihood of dislodging fragments of the clot.

Ordinarily, poor general condition of a patient is a deciding factor against any form of surgery. However, in cases of pulmonary embolism from venous thrombosis, even the patient who appears hopelessly ill is a candidate for ligation of the affected vein. Many of our patients were operated upon when they were extremely ill as the result of multiple pulmonary emboli. The danger of another episode of embolism seemed greater than the strain of operation. There were no deaths attributable directly to the operation.

In each of forty-five cases, including multiple operations, one femoral vein was ligated. In four of these a thrombus was removed at the time of operation. In six additional patients both femoral veins were ligated at the same operation. In almost every instance the point of ligation was just distal to the entrance of the saphenous vein into the femoral. In none of these cases have we seen any evidence of subsequent thrombosis of the saphenous vein. The femoral vein was explored only in those cases in which it was believed from the clinical picture that the thrombus had not extended above the inguinal ligament. In a few cases the femoral vein was explored and found to be inflamed. The process therefore was older than we had anticipated. In such cases the first incision was closed and the common iliac vein was ligated.

The external iliac vein was ligated in only six cases. This vein is very accessible, but because of the problem of collateral circulation,¹⁵ ligation at this level is less desirable than at the common iliac.

Counting the cases in which multiple operations were done, a common iliac vein was ligated twenty-nine times. Ligation was done fourteen times on the right side, fifteen times on the left side. In eight instances a thrombectomy was performed at the same time. All of these operations were done by means of an extraperitoneal approach to the veins. We have found that the left common iliac vein can almost always be exposed satisfactorily for proper exploration of the lumen of the vein preceding ligation.

In six cases it was necessary to ligate the inferior vena cava; four times because of thrombosis in both iliac veins, and twice because of extension of inflammation from the left common iliac vein to the wall of the vena cava. Pulmonary embolism had occurred before ligation in all of these cases. In five instances the thrombosis originated in the tibial veins. The sixth case was one of typical iliofemoral thrombophlebitis which had seemed to be responding well to treatment by means of re-

peated infiltration of the lumbar sympathetic ganglia with procaine solution. After all evidence of the inflammatory phase of the disease had subsided, the patient developed pulmonary embolism. At operation it was found that the lower part of the inferior vena cava was inflamed and that a clot projected into its lumen from the left common iliac vein. There was no involvement of the veins of the other lower extremity.

In Table IV the types of multiple operations are listed separately. It is to be understood that in each instance the multiple operation was necessary because of obvious signs of pathology in the veins ligated. About one in every five of our patients showed positive evidence of bilateral involvement. There may have been others in which the disease was not recognized to be bilateral. We are in agreement with the thought³ that bilateral ligation probably should be done more frequently.

RESULTS OF OPERATIVE THERAPY

As stated earlier, the objects of treatment of thrombosis of the deep veins of the lower extremity are to prevent pulmonary embolism, to limit propagation of the thrombus, and to correct the local impairment of circulation. Evaluation of the results of operative therapy must be made in the light of these objects.

There is no question that ligation diminishes the likelihood of pulmonary embolism. In forty-five cases in which pulmonary embolism had not preceded ligation, there was no instance of embolism subsequent to ligation. In view of the fact that Welch and Faxon¹⁴ estimate that the chances of developing pulmonary embolism in the type of venous thrombosis under discussion are about one out of three, this is indeed a significant achievement. Of thirty-nine cases in which pulmonary embolism occurred before ligation, nine patients also had embolism after ligation. In the light of the experience gained in the management of these cases, most of the postligation embolisms could have been prevented. In five instances the source of embolism was the opposite, unligated side. In the other four the origin of the embolus was in the femoral vein above the point of ligation, and in three of these the vein showed definite inflammation at and above the point of ligation. Therefore, in eight of the nine cases of postligation embolism, the recurrent embolism was the result of inadequate surgical treatment rather than a fault of the principle of treatment.

Ligation of a deep vein at a normal segment above the level of thrombosis will unquestionably trap the clot already formed and will prevent the formation of a thrombus above the point of ligation in almost every case. Thus, only one out of eighty-four patients developed thrombosis above the level of ligation when these principles were observed. In addition, it has been our impression that after ligation there is less tendency of the thrombus to extend in the veins below the level of ligation than when the disease is al

fore, surgical treatment effects a saving in patent venous channels which will be available for the development of collateral circulation.

Ligation cannot be expected to remove the venous obstruction that has already developed. In many instances, it temporarily increases the obstruction. The degree to which this local impairment of circulation will be corrected depends upon the adequacy of the collateral circulation. This in turn depends upon the extent of the thrombosis and the number and size of veins available as collateral channels. The point of ligation also affects the efficiency of the collateral circulation. We have found that patients in whom the inferior vena cava or common iliac vein is ligated usually develop a more complete collateral circulation than those in whom the external iliac or femoral vein is ligated.

The functional restoration of the involved extremity after ligation is excellent. Pain, which is a common complaint before ligation, quickly disappears. In some cases the relief of pain is dramatic. Vasospasm, if present, is usually abolished very promptly. However, in this series, ligation provoked arterial spasm in three cases, which are to be the subject of a separate report.¹⁷ Edema, a very frequent finding before operation, is sometimes temporarily increased following ligation. The edema usually subsides after a few days of rest and elevation of the extremity. It has generally been our policy to have the patient wear an elastic stocking when activity is resumed. This is worn until edema no longer develops as a result of activity. It has been of special interest to us to follow the progress of the cases in which the inferior vena cava was ligated. The complete restoration of function in these cases that were seemingly hopeless at the time of operation has been most gratifying.

In this series of eighty-four cases there were seven deaths. Three resulted from recurrent pulmonary embolism, originating in the unoperated extremity. Four patients died from the combination of their original diseases and preoperative multiple pulmonary embolism.

SUMMARY AND CONCLUSIONS

1. We have presented data on eighty-four cases of thrombosis of the deep veins of the lower extremity treated by ligation of the affected veins.
2. A total of ninety-eight ligations were performed. The sites of ligation were the inferior vena cava (six times), common iliac vein (twenty-nine times), external iliac vein (six times), and femoral vein (fifty-seven times).
3. In forty-five cases in which ligation was performed before the development of pulmonary embolism, there were no instances of this complication. In thirty-nine cases in which the operation was done after at least one episode of pulmonary embolism, there were nine cases of postligation embolism.
4. There were no deaths as a result of operation.

5. Ligation therapy effectively limits the propagation of a thrombus, prevents pulmonary embolism, and permits more rapid and more complete restoration of function of the involved extremity.

REFERENCES

1. Ochsner, A., and DeBakey, M.: Thrombophlebitis; The Role of Vasospasm in the Production of the Clinical Manifestations, *J. A. M. A.* 114: 117, 1940.
2. Veal, J. R., and Hussey, H. H.: The Pathologic Physiology of the Circulation in Acute Thrombophlebitis and the Post-Thrombotic Syndrome, *Am. Heart J.* 23: 390, 1942.
3. Allen, A. W., Linton, R. R., and Donaldson, G. A.: Thrombosis and Embolism, *Ann. Surg.* 118: 728, 1943.
4. Fine, J., Frank, H. A., and Starr, A.: Recent Experiences With Thrombophlebitis of the Lower Extremity and Pulmonary Embolism, *Ann. Surg.* 116: 574, 1942.
5. Barker, N. W., Nygaard, K. K., Walters, W., and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism; II. Predisposing Factors, *Proc. Staff Meet., Mayo Clin.* 16: 1, 1941.
6. Hunter, W. C., Sneed, V. D., Robertson, T. D., and Snyder, G. A. C.: Thrombosis of Deep Veins of Leg: Its Clinical Significance as Exemplified in 351 Autopsies, *Arch. Int. Med.* 68: 1, 1941.
7. Hampton, A. O., and Castleman, B.: Correlation of Postmortem Chest Teleoroentgenograms With Autopsy Findings, *Am. J. Roentgenol.* 43: 305, 1940.
8. Ochsner, A., and DeBakey, M.: Therapeutic Considerations of Thrombophlebitis and Phlebothrombosis, *New England J. Med.* 225: 207, 1941.
9. Dock, W.: Evil Sequelae of Complete Bed Rest, *J. A. M. A.* 125: 1083, 1944.
10. Gilbert, N. C., Trump, B. S., and de Takats, G.: Effect of Digitalis on the Clotting Mechanism, *J. A. M. A.* 124: 736, 1944.
11. Walsh, B. J.: Personal Communication.
12. Veal, J. R.: Prevention of Pulmonary Complications Following Thigh Amputations by High Ligation of Femoral Vein, *J. A. M. A.* 121: 240, 1943.
13. Homans, J.: Medical Progress: Diseases of the Veins, *New England J. Med.* 231: 51, 1944.
14. Welch, C. E., and Faxon, H. H.: Thrombophlebitis and Pulmonary Embolism, *J. A. M. A.* 117: 1502, 1941.
15. Homans, J.: Deep Quiet Venous Thrombosis of the Lower Limb; Preferred Levels for Interruption of Veins; Iliac Sector or Ligation, *Surg., Gynec. & Obst.* 79: 70, 1944.
16. Barker, N. W., Nygaard, K. K., Walters, W., and Priestly, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism; IV. Location of Thrombosis: Relation of Thrombosis and Embolism, *Proc. Staff Meet., Mayo Clin.* 16: 33, 1941.
17. Veal, J. R., and Hussey, H. H.: Arterial Spasm Following Ligation of Major Veins of the Lower Extremity. (To be published.)

THE SURGICAL THERAPY OF THROMBOSIS OF THE DEEP VEINS OF THE LOWER EXTREMITIES

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THE most important achievement of the past few years in relation to pulmonary embolism is the growing realization that embolism occurs nearly always as a consequence of venous thrombosis in the large deep veins distal to the inferior vena cava. After Murray and Best¹ reported favorably on the administration of heparin to forestall the occurrence of thrombosis or embolism, this therapy acquired widespread popularity, but the expense and considerable annoyance to the patient incident to its administration led to its partial or complete abandonment among the advocates^{2, 3} of dicoumarin, which is cheap and given by mouth. Simultaneously, with the acceptance of these modes of therapy, a surgical approach to the problem came to the fore, largely owing to the observations of Homans,⁴ who among American surgeons at least appears to be the first to have deliberately ligated the common femoral vein to forestall the discharge of an embolus. There followed a number of contributions⁵⁻⁹ from various clinics on the virtues of the more or less routine adaptation of Homans' maneuver and these clinics have, to date, persisted in this surgical approach in preference to the use of either heparin or dicoumarin.

Statistical data on the prophylactic value of any and all of these methods are of dubious validity because of the impossibility of assessing the incidence of venous thrombosis in the patients studied, since it is now quite clear from autopsy evidence that a large percentage of people have this condition without subjective or objective evidence of its presence. Moreover, an unfortunately high percentage of infarctions and fatal embolisms occur in the absence of all signs of the thrombosis responsible for them. What remains as a basis for selection of one of the three methods of therapy is perhaps the clinical impression of the efficiency of these agents once the thrombosis is known to exist. Those who prefer the surgical approach do so usually because of the dangers or demonstrated futility of heparin or dicoumarin in individual instances. For our purpose it will suffice to refer to two recent reports on dicoumarin. Evans³ recommends it as the method of choice in spite of the fact that of fifty-five patients to whom it was given, eight developed postoperative hemorrhage sufficient to cause death in two and in spite of the fact that two patients discharged emboli (one of which was fatal), one during the administration of dicoumarin and one after the administration was stopped. Barker and co-workers² likewise urge the

adoption of dicoumarin even though hemorrhage occurred in some 10 per cent of the cases in which it was given. That similar experiences have occurred from the use of heparin can be testified to by those who have given it with a critical eye to its effectiveness as well as its safety. One need not here stress the considerable energy and constant watchfulness necessary for effective maintenance of a delayed coagulation time, as well as the frequent failure to achieve the desirable level with uniformity because of unpredictable responses to predetermined dosage.

In making a choice between these drugs on the one hand and surgical treatment on the other, it is appropriate at this point to discuss also the shortcomings of surgical treatment. These have been discussed by Homans,¹⁰ Fine, Frank, and Starr,⁹ and others. The fluidity of the present status of surgical therapy derives from them and they can best be illustrated by pointing up the lines upon which those who prefer this method agree and those upon which they differ.

Quiet Venous Thrombosis (Phlebothrombosis) Versus Thrombophlebitis.—The distinction implied in this heading¹⁰ is stressed with some emphasis by Ochsner and DeBakey¹¹ and concurred in by Homans,¹⁰ who states that thrombophlebitis involving the femoro-iliac system is a fully obstructing type of thrombosis accompanied by outspoken perivascular inflammation and swollen lymph nodes, in which the thrombus is so firmly attached that embolism need not be feared. "The greater the swelling and discomfort the less the danger that a soft detachable mass exists." "And if . . . embolism actually occurs, one can be reasonably certain that it comes not from the vein of the swollen limb but from the other or innocent appearing leg." In quiet venous thrombosis, according to Homans, a soft nonobstructing detachable clot exists and perivascular inflammation is not an outspoken feature; therefore the danger of embolism is great. In the strict pathologic sense such a distinction has validity only in that there are gradations from case to case in the amount of adherent thrombus, soft loose clot, and perivascular inflammation. It is our opinion that from the clinical viewpoint this distinction is dangerous if it is relied upon as a basis for interference or noninterference for the prevention of embolism. For our experience convinces us that one cannot tell in any given case whether or not a soft clot is present regardless of the estimated degree of thrombosis present. That loose clot can be present in the full blown clinical condition of phlegmasia alba dolens is illustrated by the following recent cases:

CASE REPORTS

CASE 1.—I. R., a woman, aged 35 years, developed an ischio rectal abscess two weeks following discharge from the hospital after a cholecystectomy. Two weeks after drainage of the abscess she complained of severe pain in the left calf which was swollen and tender. Three hours later she developed tachycardia, substernal distress, and pain in the right posterior chest aggravated by breathing or coughing. Four hours later she showed massive edema and moderate cyanosis of the entire leg, a tense bulging tender calf area, and tenderness along the entire femoral vein, with evidence of inflammatory swelling in the femoral glands. Immediate explora-

tion of the left pelvis extraperitoneally showed marked acute perivascular inflammation, acute lymphadenitis, spasm of the iliac artery, and a tense bulging iliac vein, from which a long soft unattached clot was sucked out. The right common femoral vein was ligated also, but no inflammatory reaction was seen in this region. Three weeks later the right ankle was slightly edematous; otherwise both legs were normal, though cool, and with a slight cyanotic tinge of all the toes.

It may be argued that the embolus came from the right lower leg veins and not from the left iliac vein. But the proved presence of a long soft loose clot in the left iliac is impressive evidence that acute thrombophlebitis with a "fully obstructed venous system" cannot be dismissed as free from the danger of embolism and that the safest course is to assume nothing as to the precise nature of the clot or thrombus and its embolic potentialities until it is exposed to view.

CASE 2.—A 28-year-old woman who had been gotten out of bed on the third day after cesarean section complained of pain in the left thigh. The next day examination showed a small area of tenderness and induration in a tributary of the internal saphenous vein. There was no fever. Two days later the entire leg was found swollen from ankle to groin. The leg was cyanotic, especially when dependent. Tenderness was present in the calf, along the femoral vein, and in the groin. Exploration revealed plastic exudate about the femoral sheath, the femoral artery was constricted, and the femoral veins, both deep and superficial, were distended with thrombus. The femoral lymph glands were swollen. A long soft non-adherent clot was aspirated from the iliac vein through an incision in the common femoral. Older thrombus was present distal to the opening in the vein. An uneventful convalescence followed.

CASE 3.—S. K., a 36-year-old man, thirteen days after an abdominoperineal resection, developed pain and swelling in the left calf. The next day the entire leg up to the groin was greatly swollen, the lower leg was tense. Distended superficial veins, a positive Homans' sign, and tenderness in the groin and along the femoral vein were present. The vein was exposed and a large soft clot extending proximally well up into the common iliac was sucked out and the vein divided. There was considerable perivascular inflammatory reaction and the femoral lymph nodes were edematous and hyperemic. Slow but steady resolution took place so that one month thereafter all signs of the process had vanished.

The foregoing three examples of femoro-iliac thrombosis could not be distinguished from classical so-called milk leg. There is little doubt that the size of the soft clot in all these patients, if fully detached, could have caused fatal embolism. There is also little doubt that if the clot had not become loosened it would have been converted in time to an adherent thrombus. Hence it would be more correct in our view to say that the longer the patient has had femoro-iliac thrombosis, the less the likelihood of a fatal embolism. But if the condition is detected early enough one cannot say that the clot is or is not adherent. Accordingly, we find it expedient, except in long-standing cases, to explore every patient without making a distinction which may work to the greater detriment of the patient than would exploration of the vein.

Unilateral or Bilateral Ligation.—The literature is now replete with pathologic data on the astonishing frequency with which the process

of thrombophlebitis of the lower extremities occurs bilaterally. The more thoroughgoing the investigation is of the deep veins, the higher the frequency, so that there is little doubt that at least one-half of all patients with the disease have it on both sides. Since the disease is commonly devoid of all signs of its presence, the practice of ligation on both sides, when only one side is obviously involved or when infarction has occurred, irrespective of the apparent extent of involvement of either side, is the safest prophylactic measure against embolism.

Venography.—In a previous statement of the problem^a we urged venography on two grounds: (a) to determine the presence of the disease and (b) to determine the proximal extension of the process in order to define the level of attack upon the clot. We have with increasing experience come to find the value of venography much more limited than we had believed, for the following reasons:

1. The clinical signs of the disease were sometimes present in the absence of venographic evidence.

2. Spastic irregularity or spastic obliteration may occur and be impossible to distinguish from organic occlusion.

3. When one side is clearly involved and the other side by venography appears not to be, the avoidance of ligation of the uninvolved side has not infrequently been followed by the necessity of doing the ligation on this side because of the subsequent development of unmistakable evidence of the disease by venography or signs and symptoms or both. Meanwhile, the avoidance of the ligation may have allowed infarction to take place by embolism from that side.

The Level of Surgical Attack.—Embolism occasionally occurs even when bilateral femoral ligation is performed. This is not difficult to understand if a clot present above this level is overlooked, incompletely removed, or forms after ligation. The likelihood of this occurrence is minimal when the process on both sides is confined to the veins below the knee or well below the common femoral. It is maximal when the clot is not entirely removed or overlooked above the site of ligation or in excessively thrombophilic individuals who continue setting up new foci proximally. An example of the extraordinarily bizarre possibilities is illustrated in Case 4.

CASE 4.—N. W., aged 32 years, was said to have suffered from grippe and sinusitis complicated by an atypical rheumatic syndrome for a period of five months, during which he was alternately in and out of bed. He then began coughing and showed signs in both lower lobes suggestive of bronchopneumonia. For several weeks before admission to the hospital he coughed up streaks of blood and for one week bright red blood in small amounts frequently. During this week he had stabbing pain on respiration along the right costal margin and began having pain in the left leg. When seen by one of us he showed little local disturbance in this leg except for tenderness along the femoral vein and in the calf, and slight edema of the

whole leg, chiefly below the knee. The right leg was entirely devoid of signs or symptoms. Under spinal anesthesia the left external iliac vein was exposed. Perivascular inflammation and swollen lymph nodes were present. The vein was distended and tense and a large soft clot was extracted from the distal and proximal extensions of this vein. When the vein was entirely empty and free flow from above was obtained by suction, it was ligated and divided between ligatures. The right common femoral vein was then exposed. No inflammation was seen around this vein or in the femoral glands and the vein was free of clot. It was ligated in continuity and the patient returned to bed. One hour later the patient was in shock and evidence of massive embolism was present. Eight hours later death occurred and autopsy disclosed massive pulmonary embolism. The embolus had become detached from an isolated area of thrombus confined to the proximal few inches of the right common iliac vein with no involvement of the deep venous system distal to this segment. The fractured end of the clot fitted into that of the thrombus still in situ. On the left side a soft clot was found in the lower left leg in the popliteal vein.

The probability of identifying this thrombus by venography is remote. Even with knowledge of its presence nothing less than ligation of the vena cava would have prevented it. But if we are to do anything less than ligation of the vena cava at the bifurcation whenever ligation is to be done at all, much more experience than is at present available must be had on the consequences of this procedure. Persistent edema of the extremities and occasional shock due to sudden increase in tension of the distal venous system with consequent local loss of plasma into the tissues may prove to be not uncommon complications of this procedure. Such plasma loss may be expected to be only temporary since the caval block will be by-passed effectively, mainly via the intraspinal venous sinuses.

Until such experience is extensive enough, the appropriate attitude toward the problem will be to confine ligation to both common femorals above the profunda, to one common iliac and one femoral, or, if both common iliaes require ligation, to do the simpler procedure, that is, vena cava ligation.

What are the indications for choosing among these alternatives? While the approach to the iliac is certainly more of a surgical undertaking than that to the femoral, it is well borne by even very sick patients. Both common iliac vessels can be exposed through the same incision.¹¹ There are sufficient cases in which the operator, having cleared the iliac as well as possible through an opening in the femoral vein, cannot feel satisfied that he has not left some clot. It is also plain that even complete evacuation of all clot, if mixed with some adherent thrombus, must leave damaged intima which permits the reformation of both thrombus and clot. It is no longer sufficient, therefore, to approach involvement of the iliac vein by femoral phlebotomy. A direct approach is essential. An index to the necessity of direct exposure of the iliaes is any or all of the signs indicating their involvement, which are as follows: (1) swelling of the thigh, mild, moderate, or severe; (2) pain in the groin and tenderness in the groin or along the upper part of the

femoral vein; (3) swelling of the femoral lymph nodes; (4) cyanosis of the thigh; (5) dilatation of the superficial veins of the thigh. But even in the absence of all these signs and symptoms, one may find involvement of the iliacs when the femoral vein is exposed. If, on approaching this vein, there is perivenous inflammatory reaction, involvement of the iliac is likely and a shift in surgical approach should be undertaken, if one is not clearly beyond the clot at the site of phlebotomy.

Ligation of the common femoral vein is the method of choice in the presence of signs indicating involvement limited to the deep veins below the knee or if pulmonary embolism has occurred, even in the absence of all signs of thrombophlebitis.

In a previous communication⁹ it was pointed out that fatal embolism has occurred from thrombosis of the vena profunda femoris when it has been spared by ligation of the superficial femoral vein. We persist in this view regardless of how innocuous the profunda may seem, for only a short segment of it can be visualized. The greater likelihood of edema after blocking the common femoral rather than the superficial femoral is a small consideration in view of the greater safety of the former.

While edema, cyanosis, and pain may persist or even increase after iliac or femoral vein ligation, it is impossible to determine how persistent these phenomena might have been had no ligation been done, for the operation may be undertaken without knowing whether the disease is in the florescent or deflorescent phase in a given individual. Our experience supports the statement of Homans¹⁰ that edema due to blocking flow by ligation is seldom as pronounced when the iliac is interrupted as when the common femoral is interrupted. The postligation edema, whatever its cause, is of only minor consequence in the consideration of the best level, that is, the safest level for ligation. On the score of safety we refer primarily to the certainty of blocking the potential embolus and secondarily to the risk of the procedure itself. Many hundreds of ligations have now been done, including the external and common iliac veins and the vena cava just above its bifurcation. Those familiar with the techniques involved can testify to the relative innocuousness of these procedures, at least compared to the dangers such procedures are intended to forestall. In our own experience we cannot account for a single fatality clearly attributable to the procedure itself.

As to the effectiveness of these procedures in preventing embolism we will, along with others, readily admit the occasional occurrence of infarction and, rarely, of fatal embolism following operation. Almost always this has occurred because the ligation was unilateral or at too low a level and occasionally after what appeared to be a quite adequate level. It is for this reason that vena caval ligation may come to occupy a significant place in the prophylaxis of embolism.

Age.—It is quite clear that no age is exempt from deep thrombophlebitis of the lower extremities and that while it is rare in patients

under the age of 20, it is sufficiently common under the age of 40 to leave one without assurance that an embolus will not follow phlebitis in a young adult.

No adult who is confined to bed for any reason, whether for a medical or surgical condition, may be regarded immune to the disease. While it is commoner in elderly patients, for example, those with prostatic disease; in people with varicose veins, especially those who have already had a previous deep phlebitis; in elderly patients with coronary disease; in those with carcinoma of the tail of the pancreas; and after a low-thigh amputation, there is no guide which permits relaxation from close observation for the presence of phlebitis, if fatal embolism is to be avoided.

From the foregoing discussion one is aware that the present status of surgical therapy is still confused and leaves much to be solved in attaining the ideal prophylaxis against embolism. Indeed, even when surgical therapy is intelligently applied, occasions will arise when heparin or dicoumarin may be correctly employed in addition, unless perhaps the vena cava itself has been ligated. This will be the case if infarction continues and no other surgical procedure is indicated or deemed wise. But these anticoagulants should even then be used with a clear understanding of their limitations, for it is not to be expected that every patient will be assured of recovery from threatened embolism if all three methods are employed.

Since the occurrence of deep thrombophlebitis is so clearly related to inactivity and recumbency, the prophylaxis against the development of this disease has included the practice of early, active, and continued motion in bed, and as early rising as possible for surgical and non-surgical patients. For the past year we have gotten most patients out of bed within a day or two after operation, not excepting such patients as have had gastrectomy or abdominoperineal resection. We have no less than five patients in this series who developed thrombophlebitis nevertheless. It is perhaps appropriate here to remark that being up in a chair and walking occasionally during the first few postoperative days is not equivalent to early active motion of the extremities.

SUMMARY AND CONCLUSIONS

1. Heparin and dicoumarin are useful but not thoroughly dependable agents for the prophylaxis of pulmonary embolism. Their use is furthermore complicated by the occurrence of hemorrhage in wounds and elsewhere, which has occasionally proved fatal.

2. The surgical prophylaxis of pulmonary embolism is the procedure of choice among those who prefer a more direct and immediately applicable method for blocking the discharge of an embolus. The risks of ligation of the common femoral, the iliacs, and possibly also the vena cava are minimal and are accompanied by little postoperative dis-

turbance except for transitory increase in edema in occasional instances. This increase in edema is less likely to occur when the common iliac vein is ligated.

3. The selection of the level of ligation is made on the basis of the evidence of the extent of involvement: (a) the common femoral vein is ligated when thrombophlebitis is limited to the veins below the knee or when pulmonary embolism has occurred in the absence of all signs of involvement; (b) the common iliac is ligated when thrombophlebitis involves the common femoral, external, or common iliac veins; (c) the vena cava is ligated when the indications are that both common iliacs require ligation.

4. Since the frequency of bilateral involvement is high, bilateral vein ligation is generally indicated.

5. The occurrence of spastic narrowing or obliteration of venous channels limits the diagnostic usefulness of venography.

6. The distinction between quiet venous thrombosis and full-blown thrombophlebitis, that is, phlegmasa alba dolens or milk leg, is not a dependable means of deciding when a clot is detachable and when it is not. Therefore, exploration of most cases of so-called milk leg is advisable.

7. Early mobilization after operation does not provide full security against the development of thrombophlebitis.

REFERENCES

1. Murray, G. D. W., and Best, C. H.: Heparin and Thrombosis, Present Situation, *J. A. M. A.* 110: 1, S. 1938.
2. Barker, N. W., Allen, E. V., and Waugh, J. M.: The Use of Dicoumarol in the Prevention of Postoperative Thrombophlebitis and Pulmonary Embolism, *Proc. Staff Meet., Mayo Clin.* 18: 102, 1943.
3. Evans, J. A.: Anticoagulation Therapy of Postoperative Venous Thrombosis and Pulmonary Embolism, *S. Clin. North America*, June, 1944.
4. Homans, J.: Thrombosis of Deep Veins of Lower Leg Causing Pulmonary Embolism, *New England J. Med.* 211: 993, 1934; *Circulatory Disease of Extremities*, New York, 1939, The Macmillan Company; Exploration and Division of the Femoral and Iliac Veins in the Treatment of Thrombophlebitis of the Leg, *New England J. Med.* 224: 179, 1941.
5. Sears, J. B.: Experience With Femoral Vein Ligation for Prophylaxis of Postoperative Pulmonary Embolism, *New England J. Med.* 224: 108, 1941.
6. Welch, Claude E., and Faxon, Henry, H.: Thrombophlebitis and Pulmonary Embolism, *J. A. M. A.* 117: 1502, 1941.
7. Fine, J., and Sears, J. B.: The Prophylaxis of Pulmonary Embolism by Division of Femoral Vein, *Ann. Surg.* 114: 801, 1941.
8. Allen, A. W., Linton, R. R., and Donaldson, G. A.: Thrombosis and Embolism; Review of 202 Patients Treated by Femoral Vein Interruption, *Ann. Surg.* 118: 728, 1943.
9. Fine, J., Frank, H. A., and Starr, A.: Recent Experiences With Thrombophlebitis of the Lower Extremity and Pulmonary Embolism; The Value of Venography as a Diagnostic Aid, *Ann. Surg.* 116: 574, 1942.
10. Homans, J.: Deep Quiet Venous Thrombosis in the Lower Limb; Preferred Levels for Interruption of Veins; Iliac Section of Ligation, *Surg., Gynec. & Obst.* 79: 70, 1944; *Medical Progress; Disease of the Veins*, *New England J. Med.* 231: 1944.
11. Ochsner, A., and DeBakey, M.: Therapeutic Considerations of Thrombophlebitis in Phlebothrombosis, *New England J. Med.* 225: 207, 1941.
12. Murray, G.: Aortic Embolectomy, *Surg., Gynec. & Obst.* 77: 157, 1943.

INTRAVENOUS CLOTTING

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INTRAVENOUS clotting is of great significance because of its complications and its sequelae. Whereas previously all forms of intravenous thromboses were considered as being similar, it is our conviction that from etiologic, clinical, prognostic, and therapeutic standpoints, it is necessary to distinguish between two major types, thrombophlebitis and phlebothrombosis.^{52-55, 96} The clotting in thrombophlebitis is the result of injury to the vascular endothelium from mechanical trauma, chemical injury, or bacterial invasion, whereas in phlebothrombosis, the intravascular thrombus formation is due to alterations in the cellular and fluid constituents of blood, which increase the clotting tendency, and to venous stasis. The clinical manifestations of the two types of intravenous clotting are entirely different. In thrombophlebitis, the symptoms are marked, whereas in phlebothrombosis there are few, if any, clinical manifestations. The prognostic significance of this differentiation lies in the fact that in thrombophlebitis, unless there is suppuration which is rare, the clot is firmly adhered to the vein wall and therefore is not likely to become detached and result in embolism. Because of the associated inflammatory process, it is usually accompanied by profound arterial spasm resulting in edema which may persist and cause prolonged disability. On the other hand, the coagulum in phlebothrombosis is loosely attached to the vein wall and can be detached easily, resulting in embolism. The therapy of the two conditions is also different. Because the clinical manifestations in phlebothrombosis are due to associated vasospasm, the relief of vasospasm usually results in prompt relief of symptoms and subsidence of the lesion. On the other hand, in phlebothrombosis, either thrombectomy or the ligation of the vein above the thrombus is imperative in order to prevent a possible fatality from pulmonary embolism.

As a result of any trauma, changes may occur in the blood constituents which favor clotting. This is undoubtedly a protective mechanism and at times is necessary in order to prevent excessive hemorrhage. Unfortunately in many instances, the increased coagulability of the blood is undesirable and is the predisposing factor in the production of intravenous clotting. The trauma may be accidental, the result of an operation or delivery, or may follow the invasion of tissue by microorganisms or neoplastic tumors. The principal precipitating factor in intravenous clotting and the one which is of importance in the determination of the site of the involvement is circulatory retardation, because as a result of slowing of the blood stream in an individual in

whom there is an increased clotting tendency, intravenous thrombosis is likely to occur. Other predisposing factors are cardiovascular disease, advancing age, seasonal variation, constitutional diathesis, obesity, debility, varicosities, excessive smoking, anemia, and foci of infection. Ophüls and Dobson⁶⁴ stated that cardiac disease was present in 52 per cent of their cases of thrombosis and embolism, and Putnoky and Farkas¹⁰⁰ found that approximately 90 per cent of their ninety-one patients with pulmonary embolism had cardiovascular disease at the time of the fatal seizure. Burke¹⁸ states that of a total of 648 cases of intravascular clotting, 444 were associated with cardiac disease. His findings emphasize further the importance of cardiovascular disease in the development of thrombosis because there were 218 patients who developed thrombosis after escaping it following a previous operation. Intravenous clotting is particularly likely to occur in older persons, probably because of circulatory retardation subsequent to cardiac weakness and also to degenerative changes within the vascular tree, both of which predispose to intravenous clotting. Ewald²⁷ states that venous thrombosis is exceptional in young persons and occurs only when there is a circulatory disturbance. According to Stieh¹¹⁸ 83 per cent of his patients who had embolism were past 40 years of age, 66% per cent past 60, and 20 per cent past 70. Allen, Linton, and Donaldson² observed 202 cases in which femoral interruption was necessary for intravenous clotting; 81 per cent of the patients were past 40 years of age, and only 19 per cent younger than 40. Fifty per cent were between the ages of 50 and 70.

There is considerable variation in the incidence of intravenous clotting according to the seasons and according to the locality.⁸⁴ Generally, intravenous clotting occurs more frequently during the spring and winter months than during the summer months, and the incidence is definitely higher in the northern clinics than in the southern ones. The average incidence in the northern states is 0.74 per 100,000 population as contrasted with 0.41 per 100,000 population in the southern states. According to Faure,²⁹ the greatest incidence of thrombosis is from December to February. He believes that grippal infections are responsible for this increase. Probably the seasonal and the geographic variations are due to the vasospastic effect of cold and its effect on the blood flow. Another factor which predisposes to intravenous clotting, probably because of its vasospastic effect, is smoking. As a prophylactic measure we believe it is desirable for patients who are to have an extensive operative procedure to refrain from smoking for a number of days before the contemplated operation and for approximately ten days postoperatively.⁸⁶ Intravenous clotting frequently occurs in certain families, so that a constitutional diathesis to this condition cannot be denied. As emphasized by many observers, the type of individual who is likely to develop an intravenous clot is fat, pale skinned, asthenic, and weak muscled. The tendency is an inherited one and recognition of the con-

stitutional disposition is of importance from a prophylactic standpoint, in order that measures can be instituted to prevent thrombosis. Obesity also is a predisposing factor. Henderson³⁹ found that the average weight of patients with thrombo-embolism was thirteen pounds greater than normal. Barker and his co-workers⁶ state that 4 per cent of patients who weighed less than 200 pounds developed thrombo-embolism, whereas 8 per cent of those weighing more than 200 pounds developed the same complication. In 3,680 patients on whom intestinal operations were done, thrombo-embolism occurred in 3.2 per cent of those who weighed less than 200 pounds and in 7.1 per cent of those who weighed more than 200 pounds. Of 156 postoperative fatalities studied by Snell,¹¹⁴ the cause of death was thrombo-embolism in 30.7 per cent. Debility and anemia are predisposing factors in intravenous thrombosis. In the former, probably the increased coagulability of the blood, and the decreased cardiac tone in the latter predisposing to circulatory retardation are responsible for the intravenous clot. Anemia predisposes to intravenous clotting because of two possible causes. First, as emphasized by Drinker, Drinker, and Kreutzmann,²⁶ following hemorrhage there is a relative increase in the cellular elements of the blood which increases its coagulability, and, second, anemia may predispose to thrombosis because of its secondary effect on the cardiovascular system resulting in diminution of cardiac tone which favors circulatory retardation. Likewise, polycythemia is a predisposing factor in intravenous clotting because the increased number of erythrocytes increases the viscosity of the blood which favors coagulation.

The absorption of noxious substances from traumatized cells following invasion by malignant disease increases the clotting tendency of the blood. In fact, the increased clotting tendency in malignancy is so great that it has been suggested that the increased coagulability of the blood might be used as a diagnostic test for cancer. Trousseau¹²¹ directed attention to the causal relationship of cancer and thrombosis and stated that frequently the first manifestation of an internal cancer is peripheral phlebitis. Sproul¹¹⁵ and more recently Kenney⁵³ have emphasized the high incidence of venous thrombosis as a complication of carcinoma of the body or tail of the pancreas. Sproul¹¹⁵ found that in 56 per cent of cases of carcinoma of the body or tail of the pancreas a single thrombus was present, whereas in 31.3 per cent the venous thromboses were widely disseminated. In 33½ per cent of Kenney's cases⁵³ of carcinoma of the body or tail of the pancreas there were multiple venous thromboses. Carcinoma of the head of the pancreas showed no increased incidence of venous thrombosis. It is interesting also that in Kenney's series the tumor was, in each instance, of the mucinous type. It is his belief⁵³ that these tumors secrete an abnormal substance or an excessive amount of a normal substance which is concerned with blood clotting. Sproul suggested that the increased incidence of intravenous thrombosis associated with carcinoma of the tail or body of the pancreas was due to in-

erased coagulability resulting from increased digestion of fats because of increased pancreatic secretions which in turn results in increased absorption of vitamin K from the intestine. That this hypothesis is not correct, however, is suggested by the investigations of Morton, Shearburn, and Burger,⁷⁸ who showed that the administration of an excess of vitamin K does not cause excessive thrombosis and intravenous clotting.

Of great importance in determining the site at which intravenous clotting is likely to occur, particularly in phlebothrombosis, is circulatory retardation. It is probably the principal reason why clotting usually occurs in the lower extremities because in these areas the greatest amount of vascular stasis occurs. As is well known, the movement of venous blood is dependent upon a number of factors, the chief of which are the vis a tergo through the capillaries, the negative pressure within the thorax, and the contraction of the skeletal muscles. As a result of an operative procedure, any illness, or cardiovascular disease the vis a tergo is definitely diminished. In the first instance this is due partly to decreased cardiac function, but also is due to vasoconstriction as DeBakey and Is⁸²,⁸⁶ have emphasized repeatedly. In the other two instances it is due mostly to the decrease in cardiac function. The negative pressure within the thorax is definitely less marked following a laparotomy or in severe illness than is found normally, because hypopnea is the rule. Deep breathing is likely to be painful following laparotomy particularly that involving the upper part of the abdomen, and for this reason the patient usually breathes in a shallow manner, thus favoring circulatory retardation in the venous system of the lower extremities. The relative immobility of the lower extremities while in bed is of great importance in favoring vascular stasis. Whereas the patient who has been operated upon or who is otherwise ill moves his upper extremities, he is very likely to keep his lower extremities immobile predisposing to circulatory retardation in the lower extremities. Also, patients who have had a laparotomy because of decrease in intestinal activity and associated dilatation of the gut (ileus) may have increased intra-abdominal tension. This tends to compress the abdominal veins, produce venous stasis in the lower extremities, and favor clotting. According to Neumann,⁸⁰ there are a number of anatomic structures which produce localized vascular stasis and predispose to thrombosis in the particular area, that is, the plantar veins, the veins of the calf, and the veins of the thigh. Posture may favor vascular stasis. The use of Fowler's position, particularly with the flexion of the leg on the thigh at the knee, causes stasis below the popliteal vein because of the dependency of the leg and also because of the kinking of the popliteal vein. According to Friedländer,⁸³ with the patient in the prone position vascular stasis of the lower extremity is favored because of the uphill course of the femoral vein to join the iliac at the pelvic entrance.

As previously mentioned, injury to tissue as result of an operation, an accidental trauma, a delivery, or invasion by infection or malignant disease results in increased coagulability of the blood because of absorption into the blood stream of noxious substances derived from the traumatized cells. The increased blood coagulability is the result of changes in the plasma and the formed elements of the blood. The changes in the plasma consist of increased viscosity, hypoproteinemia, hyperglobulinemia, increased fibrinogen content, increased antitryptic power, increased peptidase, increased calcium content, and decreased carbon dioxide combining power. Because of the increase in globulin and decrease in albumin there is a disturbance in the albumin-globulin ratio which is evidenced by an increased erythrocytic sedimentation rate.^{10, 17, 24, 28, 41, 54, 71, 72, 116, 117, 119, 126} The peptidase content of the plasma is an indication of the cell destruction according to vonSeemen¹¹¹ and the aseptic destruction of the cells produces a decreased blood stability and a decrease in antithrombin with an increased tendency toward clotting. Associated with this is a disturbance in the ratio of calcium and potassium ions and also a disturbance in the albumin-globulin ratio in that the globulin is increased and the albumin decreased. Lambret and Driessens⁶⁴ showed that postoperatively there is a rise in polypeptides which reaches a maximum at about the fifth day and the more prolonged, the more traumatic, and the more histolytic the operative procedure, the greater is this increase. In addition to the changes in the fluid element of the blood which predispose to clotting there are alterations in the cellular elements of the blood. Thrombocytes and leucocytes become increased, and erythrocytes become decreased. Of great importance also is the increased agglutinability of the formed elements of the blood, particularly the thrombocytes. This is probably due to a change in the electrical charge of the formed elements which results in the loss of the normal repulsion of these elements with a resultant attraction to one another. This increased agglutination tendency causes clumping and is probably responsible for the initiation of a thrombus. The change in the electrical charge of the formed elements is the result of the disturbance in the albumin-globulin ratio referred to previously.^{10, 17, 24, 28, 41, 54, 71, 72, 111, 116, 117, 119, 126} Hausser³⁸ found that the increased agglutinability of the platelets paralleled the increased tendency toward thrombosis. He found that the increased agglutination tendency of the platelets is particularly marked after hernia repair and after abdominal operations, and was greatest in older persons.

Whereas the changes in the blood and blood constituents resulting from tissue injury and associated circulatory retardation are responsible for the intravenous clotting in phlebothrombosis, in those cases in which there is an inflammatory process of the vein wall (thrombophlebitis) the clotting is due principally to injury of the endothelium by the inflammatory process. In the latter instance the inflammation of the vein

wall is usually the result of bacterial invasion, as in puerperal thrombophlebitis and in many cases of postoperative thrombophlebitis associated with febrile reaction. As emphasized by Koster⁶⁰ and Kaufmann,⁵² the microorganisms generally gain entrance to the venous system through the medium of the perivenous lymphatics. Relatively rarely the vein intima may be involved by bacteria present in the blood stream which process has been designated by Rokitansky¹⁰⁴ as secondary phlebitis in contradistinction to the primary form in which the venous involvement begins in the wall and extends to the lumen. The latter occurs relatively infrequently and is seen only in those cases in which there is an actual pyemia.

Pathology.—Whereas previously it was thought that most intravenous clotting occurred principally in the larger veins, such as the iliac and femoral, more recent pathologic studies have demonstrated that the clotting begins primarily in the more peripheral veins. Roessle¹⁰³ found in complete autopsies of 324 consecutive cases that thrombosis occurred in the deep veins of the calf in 88 persons over 20 years of age. Of this number 38 had thrombosis of the femoral vein, in 10 of whom death was due to pulmonary embolism. Neumann⁸⁰ in a similar study of 165 unselected patients dying from a variety of causes found thrombosis in 100. The foot veins were involved in 71 per cent, the leg veins in 87 per cent, and the thigh veins in 22 per cent. Solitary thrombi occurred in the calf veins more frequently than in the other veins. Solitary calf vein thrombosis occurred in 39 per cent, solitary plantar vein thrombosis in 12 per cent, and both calf vein and leg vein thrombosis in 57 per cent. In many of these the thromboses had apparently begun in the calf veins. There were no cases in which femoral thromboses occurred without involvement of the calf veins. Similar observations have been made by Bauer,⁹ Hunter and his collaborators,⁴⁸ and Frykholm.³⁶ Frykholm³⁶ in a dissection of 133 venous thromboses observed that 85 per cent were found distal to the profunda in the femoral vein and most of these were below the knee. The involvement of the left side is more frequent probably because the greatest amount of vascular stasis is on this side for definite anatomic reasons.

Thrombophlebitis may occur in normal veins or in diseased veins. The previously normal veins in which thrombophlebitis is likely to occur are: (1) the cavernous cerebral sinus following infection of the upper lip or nose; (2) lateral cerebral sinus following infections of the middle ear and mastoid process; (3) ileocolic superior mesenteric and portal veins following acute suppurative processes in the intestinal tract, especially of the appendix; (4) ovarian, hypogastric, and common iliac veins following suppurative processes in the puerperal uterus; and (5) superficial and deep veins of the lower extremities following infections of the pelvis and the lower extremity.⁹² Thrombophlebitis of the cavernous sinus fortunately occurs relatively infrequently, but is almost invariably the result of maltreatment of localized suppurative lesions

about the upper lip and nose. The absence of subcutaneous fat in the upper lip, the active muscular supply of the lip, movement of which exerts a pumping action on the venous radicles of the labial plexus, and the inability of the veins in this region to collapse are responsible for the involvement of the cavernous sinus through the facial, angular, and ophthalmic veins in cases of phlegmon of the upper lip. Thrombophlebitis of the portal veins following suppurative processes in the cecum and rectum occurs more frequently than is commonly appreciated. According to Gage, Garside and myself,⁵² thrombophlebitis of a portal vein occurs in from 0.1 to 1 per cent of all cases of acute appendicitis and in about 5 per cent of patients dying of appendiceal peritonitis. Involvement of the ovarian and hypogastric veins following uterine infections occurs not infrequently in puerperal infections and is likely to follow septic abortion. Miller⁷⁰ found in 100 reported cases of puerperal pyemia in which a vein ligation had been done and in which localization was stated, involvement occurred in the following veins: one ovarian vein, 75 times; two ovarian veins, 5 times; one hypogastric and one ovarian, 6 times; one common iliac, 8 times. The diseased veins in which thrombophlebitis is likely to occur are varicosities of the veins of the lower extremities and of the hemorrhoidal veins.

In addition to these cases of thrombophlebitis there are many other cases of thrombophlebitis which are differentiated from those mentioned by the fact that the lesions are not suppurative lesions. Thrombophlebitis involving the cavernous sinus, the lateral sinus, and the portal veins and the ovarian and hypogastric veins are usually associated with suppuration and the clinical picture is characterized by recurrent chills and the septic type of temperature. On the other hand, most cases of thrombophlebitis are caused by a nonsuppurative inflammatory process involving the deep venous system of the lower extremity. This is typified by the phlegmasia alba dolens which is so well known to clinicians. Since there is no suppuration in these cases there is no liquefaction of the clot and a septic clinical picture is not seen.

The vascular changes in thrombophlebitis can be divided into those occurring in the perivenous tissue and those in the vein wall itself. The perivenous changes consist principally of a lymphangitis. According to Koester,⁵⁹ the thrombophlebitic process is in reality a lymphangitis of the veins in which the infection is carried to the veins by means of the lymph channels. The importance of perivenous lymphangitis has been emphasized by Karsner,⁵¹ Homans,⁴³ and Homans and Zollinger.⁴⁵ As a result of the perivenous involvement, fibrinous exudation into the perivascular spaces and the accumulation of perivascular fluids resulting in edema are likely to occur. Kaneko¹⁰ was able to produce intravenous thrombi experimentally by the perivenous implantation of streptococci, staphylococci, and colon bacilli. In addition to the perivenous changes there are changes within the wall of the vein, consisting primarily of hyperemia, cellular and serous exudation, and a destruction of the

endothelium, which is probably responsible for the thrombosis. The intravascular changes which occur in thrombophlebitis consist of the development of thrombi. The clot or thrombus produced in thrombophlebitis differs from that produced in phlebothrombosis in that the former is attached to the vein wall. As Aschoff³ described, there are two types of thrombi, the white and the red, the white usually being associated with thrombophlebitis in which there is a maximum change in the wall of the vessel resulting in a deposition and agglutination of the platelets on the vessel wall. There also becomes adhered to the vessel wall in this area, leucocytes and fibrin, resulting in a white thrombus. On the other hand, in those cases of intravascular clotting in which there are few or no changes in the vascular endothelium, but in which thrombosis occurs because of stasis in the vessel together with other factors which favor coagulation, the thrombus is similar in many, if not all, respects to an extravascular clot. This is designated as a red thrombus or coagulation thrombus. It has much the same relative proportions of blood elements as are found in the circulating blood. It is not firmly attached to the vein wall as is the white thrombus, because the former is not the result of endothelial destruction. The white thrombus, because of the destruction of vascular endothelium, is firmly attached to the vein wall and has little tendency to become detached. On the other hand, the red thrombus is attached only loosely to the vein wall and it is this type of thrombotic process that is particularly likely to give rise to pulmonary embolism. In those cases of thrombophlebitis, however, in which there is suppuration resulting in liquefaction of the coagulum, portions of the thrombus may become detached resulting in septic emboli.

The clinical picture in intravenous clotting is dependent upon the lesion in the vein, and in nonsuppurative thrombophlebitis, because of the inflammatory reaction and because of the associated vasospasm resulting from impulses originating in the thrombophlebitic segment, there is diminished vascularity to the extremity producing pain, swelling, and a persistence of fever. In the cases of suppurative thrombophlebitis in which because of the liquefaction of the clot by the suppurative process portions of infected thrombi become detached, repeated chills and aseptic temperature results. In the patient with a phlebothrombosis, in whom there is no inflammatory reaction early, there are few or no clinical manifestations but because the thrombus is only loosely attached to the vein wall, detachment can occur resulting in one or more nonfatal or massive fatal pulmonary emboli. In thrombophlebitis, because of the inflammatory process in the vein wall, there is usually a pyrexia which varies in degree with the severity of the infection and the localization of the thrombophlebitic process. Everything else being equal, the more severe the infection, the more marked is the febrile reaction; and also the larger the vein involved, the greater is the systemic reaction. In addition to fever, these patients have pain in the

region of the involved vein, and swelling of the involved extremity. The classical example of deep thrombophlebitis is phlegmasia alba dolens, in which cases the pyrexia ranges from 101° to 103° F., associated with severe pain and swelling in the involved extremity. The fever in thrombophlebitis is probably due to the inflammatory reaction of the vein wall. Previously, the pain in thrombophlebitis was thought to be due to the inflammation and irritation of the vein wall, but DeBakey and I⁸⁶ have demonstrated quite conclusively that the pain is due to ischemia, as evidenced by the prompt relief of the pain following the re-establishment of the normal blood supply to the extremity by blocking the sympathetic impulses. The edema which previously was thought to be due to increased venous pressure caused by the obstructing thrombus in the main venous channel is due also to ischemia. That obstruction of the main venous channel is not the cause is evidenced by the fact that ligation of the same vein, done aseptically seldom produces edema and that in the patients treated by sympathetic anesthetization the edema associated with thrombophlebitis disappears while the clot is still present. We have shown both clinically⁸³⁻⁸⁵ and experimentally²² that the edema is secondary to severe arteriolar spasm in the homolateral extremity resulting from the vasoconstrictor impulses originating in the thrombophlebitic segment which are carried over the sympathetic nervous system. This vasoconstriction is responsible for the whiteness of the skin as designated by the term phlegmasia alba dolens. Because of the extreme vasoconstriction of the arterioles and ischemia resulting in relative anoxia of the capillary endothelium, an increased permeability of the capillary endothelium results. This permits excessive exudation of the intravascular fluid out of the vascular system into the perivascular spaces and accounts for the rapid production of edema. Once the fluid gets out of the vascular system, there is difficulty in its getting back for two reasons: first, because wound absorption is interfered with because of the increased venule pressure resulting from venule spasm, and, second, because the pump which is responsible for the movement of lymph, namely arteriolar pulsation, is lost. Although the patient with thrombophlebitis has marked symptoms there is little or no danger of embolism, because of the fixation of the clot to the vein wall, except in the case in which a propagating coagulation thrombus occurs proximal to the area of thrombophlebitis, or in the case of suppurative thrombophlebitis in which liquefaction of the clot occurs.

The patient with phlebothrombosis may have no symptoms. He usually has no pain, has little or no fever, and there is usually no swelling of the extremity. We have observed that frequently the patient has a sense of impending disaster. According to Bahls,⁴ the patient is likely to be restless. There is almost invariably tenderness over the involved vein and the calf and plantar veins are frequently the original sites. Tenderness in the calf or on the plantar aspect of the foot is of importance. Pain in the calf or popliteal area resulting from dorsiflexion

of the foot with the leg extended is of diagnostic importance as suggested by Homans.^{42a} Not infrequently there is an increasing pulse rate out of proportion to temperature elevation, which finding has been emphasized by Mahler⁷³ and DeBakey and me.⁸⁰ Mahler described this as stepladder pulse. In a suspected case the determination of the erythrocytic sedimentation rate is of importance, and is probably the result of the alteration of the albumin-globulin ratio.¹⁰ 17, 24, 28, 41, 54, 71, 72, 116, 117, 119, 126

Diagnosis.—The diagnosis of thrombophlebitis is not difficult. In fact usually the patient calls the attention of the physician to the lesion because of the pain, tenderness, and swelling. In addition to this, elevation of temperature usually signifies some lesion. There is tenderness along the course of the involved vein and in the skin of the extremity. If the involved vein is a superficial one, there is also redness in this area. On the other hand, if the deep veins are involved, the extremity is cold and whiter than normal due to the associated spasm of the arterioles. There is usually a pitting edema. Phlebothrombosis can be diagnosed definitely only by demonstrating the presence of the venous obstruction by means of visualization of the venous system (phlebography).⁸⁰ Although we originally thought that phlebography should be done in all cases of suspected phlebothrombosis, we now feel that in a suspected case of phlebothrombosis the diagnosis can be accepted and appropriate therapy instituted immediately. In any patient who has had a pulmonary embolism immediate steps must be taken to prevent further emboli because following one embolism there is the likelihood of another. Zink¹³¹ has shown that in 70 per cent of patients with fatal pulmonary embolism there was a previous nonfatal pulmonary infarct, the result of embolism. We had an opportunity to see a patient who had had five nonfatal pulmonary infarctions before curative therapy was instituted.

Treatment.—There are probably few conditions in which prophylaxis can be so readily accomplished and yet is so important as in intravenous clotting. The importance of this has been repeatedly emphasized by DeBakey and me.^{82-88, 92} Because cardiovascular disturbances with the resultant circulatory retardation are of such great importance in the development of intravascular clotting, it is imperative in any patient who has tissue injury resulting from operative, accidental, or puerperal trauma or from invasion by infection or neoplastic disease, that normal cardiovascular function be maintained or early re-established. This is particularly true in older persons in whom cardiovascular disease is more liable to occur. The value of prophylaxis is exemplified by vonJaschke's⁴⁹ results. Whereas in a series of 2,053 operations the incidences of thrombosis and fatal embolism were 1.75 and 0.6 per cent, respectively, in a comparable series of 1,362 operations in which the patients were systematically digitalized preoperatively, the corresponding incidences of thrombosis and fatal embolism were 0.9 and 0.5 per cent. Koenig⁶⁸ found that following the use of sympatol (a cardiac

stimulant) in 2,000 cases postoperatively, the incidences of thrombosis and embolism decreased from 6.2 to 0.95 per cent. Similarly, Fraendorfer³¹ observed a decrease in the incidences of thrombosis and embolism from 10.6 to 2.3 per cent and in the mortality rate from 2.3 to 0 per cent.

Circulatory stasis is favored by the vasoconstrictor action of tobacco, and for this reason it is desirable for patients who are to undergo an operative procedure to refrain from smoking for a period of a few days before any contemplated operation, and in the immediate postoperative period.⁸⁶ In this way we believe that circulatory stasis can be minimized and the precipitating effect of vasoconstriction prevented.

Of great importance from a prophylactic standpoint, we believe, is the routine use of compression bandages applied to the lower extremities from the toes to the groin.⁸⁶ It is routine in our clinic to use this measure in all patients 45 years of age and older who undergo an operative procedure. This is of value not only in patients with varicosities in whom stagnation is more likely to occur, but also in patients whose superficial veins are normal. By the application of compression bandages stagnation of the blood in the superficial veins is obviated and the blood flow in the deep venous system is increased, thus preventing circulatory retardation. The value of compression of superficial veins in intravenous clotting was first stressed by Fischer.³⁰ Leun,⁶⁹ over a nine-year period, used compression bandages prophylactically in patients in whom he feared thrombosis, such as individuals with varicosities, circulatory disturbance, or other predisposing factors. In 280 cases, 500 elastic compression bandages were applied. In three cases the treatment was a failure in that thrombosis occurred. In two of these slight thrombosis occurred because the bandage was not applied tightly enough, and the third patient died of pulmonary embolism, but the autopsy showed that the thrombus originated from a pelvic vein and not from a leg vein. In obese patients in whom an elective operative procedure is done, it is imperative that there is a reduction in weight before the contemplated operation, because obesity is an important predisposing factor to intravenous clotting.^{82, 86} Also, it is desirable that foci of infection be eliminated since they too predispose to intravenous clotting.

Another important prophylactic preoperative measure is hydration and remineralization. As many patients who are subject to operation are suffering from nausea, vomiting, or diarrhea, there is likely to be a loss of fluids and electrolytes. It is not known whether the correction of these disturbances is beneficial because of the correction of increased viscosity and dehydration or because of the detoxifying effect of the electrolytes. Prima⁹⁹ is of the opinion that administration of sodium chloride solution has a definite detoxifying action which tends to prevent intravascular clotting. Anemia and other blood dyscrasias should be corrected as prophylactic measures, since these conditions predispose

to intravascular clotting. Lockhart-Mummery⁵⁰ and Donald²⁵ directed attention to the greater likelihood of thrombosis in anemia. Donald²⁵ reported three cases of profound anemia in which the patients developed fatal pulmonary embolisms, and believed that the thromboses were to a large extent caused by the anemia. Drinker, Drinker, and Kreutzmann²⁶ demonstrated that following hemorrhage there is an increase in the cellular elements which probably increases the coagulability of the blood.

In addition to preoperative prophylactic measures, a great deal can be accomplished in the prevention of intravenous clotting during the operative procedure. Since injury to tissue is an important factor in changing the blood constituents, increasing the tendency toward thrombosis, it is imperative that trauma be reduced to a minimum. Sharp dissection and careful hemostasis, avoiding mass ligation, are of great importance. Lambret and Driessens⁶⁴ found that following an operation there was a rise in the polypeptides, which reaches its maximum on about the fifth day and that this was more prolonged, the more traumatic and the more histolytic the operative procedure. Since absorbable suture material (catgut) produces maximum tissue reaction, it is desirable that nonabsorbable suture material be used, unless there is some definite contraindication. Meade and I⁵⁵ believe from both clinical and experimental investigations that cotton is the best suture material available at the present time, because it gives the minimum amount of reaction and the best healing. The incidence of infection is lower with cotton which in itself tends to decrease tissue destruction.

The prevention or correction of dehydration and circulatory collapse during the operative procedure, both of which favor circulatory retardation, is imperative. The circulatory collapse may be the result of blood loss, chilling, or operative trauma. In many cases it is necessary to administer saline, blood, or plasma. Chilling should be prevented because by virtue of its vasoconstrictor effect it predisposes to circulatory retardation. Chilling is also detrimental in another way in that it increases the viscosity of the blood as shown by Barbour and Hamilton,⁵ who demonstrated that exposure to cold causes a loss of fluid from the vascular channels into the tissues.

Postoperatively, prophylaxis also should be practiced. Dehydration and loss of electrolytes must be corrected because, due to the loss of fluid and electrolytes from the gastrointestinal tract, an increased viscosity of the blood is likely to occur as has been demonstrated by Zarubin¹²⁸ and Bolognesi.¹³ Posture is frequently of great importance in predisposing to circulatory retardation. The placing of the patient in Fowler's position with flexion of the thigh on the abdomen and flexion of the legs on the thighs at the knees results in compression of the popliteal vessels and should be avoided. If the head-up position is desirable the patient should never be placed in a sitting position but should be kept flat on the bed. The frequently employed pillow beneath the

knees when the patient is in the supine position should not be used because it favors slowing of the blood in the legs. It is the rule in our clinic that when the patient is first returned to his room he is placed in the head-down (Trendelenburg) position in order to favor the return of the venous blood from the lower extremities to the heart. This procedure has been recommended by many others.^{8, 11, 21, 27, 33, 44, 49, 79, 107} The head-down position is maintained until the patient can actively move his extremities which by virtue of the muscular contractions forces the venous blood toward the heart. The value of the Trendelenburg position in preventing postoperative thrombosis is illustrated by Schmid's^{105, 106} experience. Prior to 1935, before the use of the position was routine, the incidence of postoperative thrombosis was 3.1 per cent whereas after elevation of the foot of the bed was instituted in all cases the incidence dropped to 0.5 per cent. The respective incidences of fatal pulmonary emboli were 0.9 and 0.3 per cent.¹⁰⁵ As soon as the patient can actively contract the muscles of the lower extremity, this is insisted upon. We have him contract the calf muscles against a resistance by either placing a foot piece at the foot of the bed against which the foot can be ventroflexed or have an attendant hold the patient's toes while he flexes his feet against the resistance. Wangenstein¹²⁴ advocated having the patient move his extremities "a thousand times a day." Reis,¹⁰¹ Richardson,¹⁰² Boldt,¹² and others^{40, 56, 61, 97, 123, 127} were early advocates of the movement of the legs while the patient is still in bed. Gamble³⁷ and deTakats and Jesser²³ have suggested the use of a bed bicycle, whereas Adams and Boehme¹ believe that the foot exercises are much preferable to the use of a bed bicycle. Kirschner⁵⁵ uses elaborate gymnastic procedures, accompanied by music and under the direction of a gymnast. The importance of mobilization is emphasized by Potts,⁹⁸ who observed that whereas thrombosis and embolism are common in patients who are confined to bed with fractures in plastic encasements, they are rare in ambulatory patients with arm, leg, shoulder, or spine fractures in similar encasements.

At the present time, there are a number of advocates of early ambulation which we have used for a number of years, although we are not as radical as many in getting our patients out of bed on the day of the operation or the first postoperative day. Unquestionably, this decreases the incidence of intravenous clotting. Campeanu¹⁹ reported 1,300 cases, many of which were severe, in which the patients were allowed to walk directly from the operating room to the ward and to take gymnastic exercises immediately afterward, including even jumping. Zava,¹³⁰ who gets his gynecologic patients up either on the first or second day, states that in more than 6,000 cases there has not been a single embolism. The value of early ambulation is emphasized by vonJaschke,⁴⁹ who found among 300 patients who were allowed up relatively late, there were 2 per cent with thromboses and 1 per cent with fatal emboli, whereas in

387 cases in which early ambulation was used the incidence of thromboses was 0.5 per cent and there were no fatal emboli. In the Essinger University Clinic from 1906 to 1912 there were 1,504 operative cases in which the patient got out of bed at the end of the second week with the incidences of thrombosis and fatal embolism of 2.63 and 1.4 per cent, respectively. In the same clinic, from 1912 to 1918, there were 2,053 operations following which the patients got out of bed between the second and fifth days with the corresponding incidences of 1.75 and 0.6 per cent. The need of getting patients out of bed relatively early is exemplified by the investigations of Smith and Allen¹¹³ in which it was shown that postoperatively, beginning on the fifth day, the circulation time was increased, and that on the tenth day it was approximately 50 per cent greater than the preoperative average. Eighty-two per cent of the individual patients showed increases of four or more seconds at some time after operation.

Another measure which favors the movement of venous blood is the increased negative thoracic pressure resulting from deep breathing. The importance of this should be emphasized to the postoperative patient because usually by the descent of the diaphragm the intra-abdominal tension is increased causing pressure on the abdominal wound and pain. Because of this the patient is likely to breathe in a shallow manner. We insist upon our patients taking twelve to fifteen deep breaths every hour during their waking hours and we much prefer this being done voluntarily. If, on the other hand, they are unable or will not cooperate, it is desirable to secure deep breathing by means of carbon dioxide inhalations.^{37, 55, 57, 82, 86} The prevention of increased intra-abdominal tension by the avoidance of tight compression bandages on the abdominal wall and the prevention of ileus is of importance in decreasing stasis of blood in the lower extremities. Increased abdominal tension also may be due to the decreased action of the diaphragm and the splinting of the abdominal wall as emphasized by Patey^{95, 96} and Frimann-Dahl.³⁵

Since vasoconstriction occurs in all cases following operation it is desirable to overcome the peripheral vasospasm by vasodilatation. This can be done by either the application of heat to the extremities or reflexly producing vasodilatation by applying heat to some other part of the body. For many years we have applied heat to the abdomen in patients who have had laparotomies because we are convinced that it exerts a beneficial effect on the gut tone. In this way we have secured reflexly vasodilatation in the extremities and have minimized circulatory retardation. Leriche,⁶⁸ Kvale,⁶³ and DeBakey and I have shown that postoperatively a peripheral vasoconstriction occurs. Smith and Allen¹¹³ also showed that postoperatively there is a definite slowing of the peripheral circulation and that this is more marked when the extremity is cold.

Anticoagulants, such as hirudin, heparin, or dicumarol, might be used prophylactically. Whereas the use of these substances probably

is not justified routinely in all patients who are operated upon, their use should be seriously considered in patients in whom there is a thrombosing tendency as determined by history of previous intravenous clotting or a history of a clotting tendency in the family. The value of anticoagulants used prophylactically is shown by Barker's⁷ results at the Mayo Clinic. Dicumarol was administered postoperatively to thirty patients, who had either thrombosis or embolism previously. None developed thrombosis or embolism although the estimated incidences without an anticoagulant in these cases were 40 per cent thrombosis or embolism and 10 per cent risk of fatal embolism. In a group of 259 patients who had had abdominal hysterectomy in which the estimated incidences of thrombo-embolism and fatal pulmonary embolism were 4 and 0.7 per cent, respectively, there were no thromboses or emboli following the prophylactic use of dicumarol. DeBakey and I² believe that the principal use of anticoagulants is as a prophylactic measure and not in the treatment of thrombosis once it has occurred, because in such instances they are of little or no value in the treatment of a pre-existing thrombus and are of value only in preventing the propagation of the thrombus. At the same time, their use is likely to give the physician a false sense of security that everything is being done for the patient and he may neglect to use those therapeutic measures which are essential. On the other hand, the use of anticoagulants is not without danger and must be carefully controlled.

Although we believe that most, if not all, cases of intravenous clotting can be prevented by the institution of appropriate prophylactic measures, patients will be seen in which actual thrombosis has occurred, and in which active therapy is necessary. Once clotting has occurred it is important to differentiate between thrombophlebitis and phlebotrombosis. In nonsuppurative thrombophlebitis, because the symptoms are the result of arteriolar spasm, the treatment consists of overcoming the vasoconstriction by anesthetization of the regional sympathetic ganglia. This is essential because as long as arteriolar spasm and resulting ischemia persist there is a persistence of the clinical manifestations which may last for months or even years. The pain and swelling are the result of ischemia. The persistence of fever also is probably due to the ischemia resulting in an interference with the normal resolution of the inflammatory process. I believe that the most efficacious way of producing vasodilatation is the interruption of the sympathetic impulses by anesthetization of the regional sympathetic ganglion with procaine. DeBakey, Burch and I² have been able to demonstrate graphically both clinically and experimentally that in thrombophlebitis a marked spasm of the arterioles and venules of the homolateral extremity occurs. There is also some spasm of the contralateral arterioles, although this is much less marked than on the affected side. Following the procaine block of the homolateral sympathetic ganglia the arteriolar pulsations return to normal and the clinical picture graphically changes.

The relief of pain is immediate, occurring as soon as the anesthesia is complete. In approximately 90 per cent of instances, the pain does not recur. In the remaining cases, however, a second injection is required to relieve the patient permanently of pain. Fever and edema disappear rapidly. The temperature returns to normal within forty-eight hours in about 65 per cent of cases. In about 5 per cent of cases the pyrexia lasts longer than eight days. The swelling of the extremity, instead of lasting for months and even years, subsides very quickly with the re-establishment of the normal blood supply, because of the normal re-establishment of the arteriolar pulsations which are responsible for the movement of lymph. In our cases, edema completely disappeared within four days in over one-half of the cases, and in only 5 per cent of cases did it last longer than twelve days. These patients can be discharged from the hospital early because of the rapid subsidence of their clinical manifestations. Sixty-two per cent of our patients were discharged from the hospital within four to eight days after institution of therapy, and only 10 per cent remained in the hospital more than twelve days.

The technique of lumbar sympathetic block has been described in detail in previous publications,^{83, 84, 86} but is, in brief, as follows: The patient is placed in the lateral recumbent position. This position is used rather than the prone position which is usually employed for the lumbar sympathetic block in peripheral arterial disease, because usually a patient with thrombophlebitis is too ill to be placed in the prone position. The thighs are flexed on the trunk in an attempt to straighten the lumbar curve. The sites of puncture in the skin are determined by taking points approximately two fingerbreadths lateral to, and on a horizontal level with, the spinous processes of the first, second, third, and fourth lumbar vertebrae on the affected side. The spinous processes are chosen because the transverse processes are on a level with them. A cutaneous wheal is made at each one of these points. Special (B.D.) 20 gauge short beveled needles, 14 cm. in length, are introduced at each point vertical with the skin surface until the transverse process is reached. The transverse process is used as a landmark, because, whereas there may be considerable difference in the thickness of the subcutaneous fat and the sacrospinal muscle in an obese, muscular man and a thin, emaciated woman, there is relatively little difference in the thickness of the bodies of their vertebra. After striking the transverse process, the direction of the needle is slightly changed, either above or below the transverse process, and the needle is inserted approximately two fingerbreadths beyond the process. The point of the needle then lies on the anterolateral surface of the body of the vertebra where the sympathetic chain lies. Through each needle, 5 to 10 c.c. of 1 per cent procaine are injected after first aspirating to determine that the point of the needle is not within the vessel. The procaine anesthetization is repeated daily as long as the patient has fever, because it is

our belief that the persistence of fever is an indication of the persistence of the inflammatory process and that as long as the inflammatory process exists in the vein there is a likelihood of vasospastic impulses being set up. Although the pharmacologic effect of procaine should last one to one and one-half hours, the physiologic effect of the anesthetization of the sympathetics lasts a good deal longer, at least twenty-four hours. Generally, two to three daily blocks are sufficient to bring about complete restitution of the process. In addition to procaine blocks of the regional sympathetic ganglia, patients with thrombophlebitis should have their extremities wrapped from the toes to groin and mobilization instituted. This is particularly important in order to prevent a propagating red thrombus proximal to the thrombophlebitic segment. If this is done there is no danger of embolism occurring in the uncomplicated case of thrombophlebitis.

Although the treatment of uncomplicated thrombophlebitis is that of conservatism as outlined, suppurative thrombophlebitis must be treated radically because of the detachment of infected emboli resulting from liquefaction of the clot. In the patient who has had a pelvic infection with the development of a septic clinical picture consisting of recurrent chills and septic febrile reaction, ligation of the venous system above the site of the involvement is imperative, because if this is not done the sepsis and fatal pulmonary embolism are likely to occur. A typical example of this is puerperal sepsis especially following criminal abortion in which the thrombophlebitic process involves the venous channels draining the uterus. In such cases rapid progression of the process with breaking off of the infected emboli is likely to result in a blood stream infection and fatality. Hunter,⁴⁷ in 1793, was apparently the first to apply measures to combat this possibility, by compressing the vein above the suppurative lesion. Lee,⁶⁷ in 1865, ligated a vein above the thrombophlebitic process in two patients suffering from this condition. In 1880, Zaufal¹²⁹ successfully ligated the internal jugular vein in the treatment of pyemia originating in the internal ear. Viereck,¹²² in 1900, showed statistically the value of vein ligation in such cases. In a collected series of 108 cases, 89 patients recovered. Freund,³⁴ in 1898, was one of the first surgeons to apply the method in gynecology. He performed ligation and excision of the thrombosed ovarian vein and broad ligament in two cases. These procedures were unsuccessful. Several years later Bumm¹⁴⁻¹⁶ and Trendelenburg¹²⁰ performed venous ligation in puerperal pyemia, the former advocating ligation by the transperitoneal route and the latter by the extraperitoneal route. Miller,⁷⁷ in 1917, collected 197 cases of puerperal pyemia treated by venous ligation. Fifteen were approached extraperitoneally and 182 transperitoneally. The gross mortality was 51.6 per cent. In 1921, Martens⁷⁴ reported eleven gynecologic cases of thrombophlebitis in which ligation of the ovarian vein as well as that of the internal or common iliac was done. In two cases the vena cava was successfully ligated.

Recovery followed in seven of the eleven cases. Collins,²⁰ Weinstein¹²³ and other members of our gynecologic service have ligated the vena cava in twenty cases of severe puerperal pyemia with recovery in all but one case. We have ligated the inferior vena cava in three cases with extensive suppurative thrombophlebitis of the pelvic veins resulting from infections in the lower extremity.

Whereas there has been considerable controversy concerning the optimum time for the ligation of the vein in suppurative thrombophlebitis, it is our belief that it must be done early, and that the high mortality rates reported by earlier observers are the result of operating upon moribund patients. Trendelenburg¹²⁰ suggested that these patients be operated upon immediately after the first chill. On the other hand, there are many who believe that one should wait until the disease has become chronic before operation. It is suggested that ligation not be done until the patient had vaccinated herself against the infection. We now believe that by procrastination the patient becomes vaccinated not against her infection but against life, because most of them die. The patient who is obviously ill, and who has recurrent chills, should be operated upon early. Otherwise a fatality is likely to occur. Whereas the operative procedure is associated with little or no risk, the advantages to be derived from it are immeasurable. As early as 1912, Huggins⁴⁶ advised exploratory laparotomy in every suspicious case when the diagnosis is in doubt, because, in his opinion, "the danger from thrombophlebitis is far more threatening than the risk of operation," if done early. If an infarction has already occurred, operation should be performed immediately and procrastination in such cases is likely to mean disaster. The absence of chills in no way precludes the possibility of a septic thrombophlebitis. Schollenberg¹⁰⁸ states that, on the basis of the material at the Zurich University Women's Clinic, in the cases in which the second chill was taken as an indication for operation, 67.4 per cent of the patients were operated upon unnecessarily and in cases in which the third chill was taken as an indication for operation, 56.2 per cent were operated upon unnecessarily. The technique of the operative procedure may vary according to the individual operator. A distinct advantage of the transperitoneal route is that it is possible to visualize and ligate all four of the veins draining the uterus or even the vena cava itself, if it is found necessary, through a single incision. This operation is associated with a greater risk, however, because of the greater shock associated with the transperitoneal approach and also because of the potential danger that infection of the peritoneum will occur from division of the infected vessel. Not only should the vessel be ligated but it should be divided, and preferably a segment should be removed. Simple ligation of the inferior vena cava is all that is necessary in those cases in which it is possible to get well above the point of involvement. We have employed proximal venous ligation of the femoral vein in five cases of suppurative thrombophlebitis of the deep

veins of the lower extremity, of the brachial vein in two cases of similar involvement of the deep veins of the upper extremity, of the ovarian vein in one case of puerperal sepsis, and of the inferior vena cava in three cases of pelvic suppurative thrombophlebitis following infection of the lower extremity, all with immediate cessation of chills and prompt recovery of the patient.⁹²

The treatment of phlebothrombosis in contradistinction to thrombophlebitis is always radical. As mentioned previously, this type of intravenous clotting is accompanied with few or no manifestations. These patients do not appear ill but they represent potential fatalities, because the clot not being attached to the vein wall is likely to become detached and result in a fatal pulmonary embolism. Unless measures are taken to prevent the clot from getting into the systemic circulation after it becomes detached, a tragedy will result. In suspected cases of phlebothrombosis and also in those cases in which a pulmonary infarct has occurred, ligation of the involved vein above the thrombus is imperative. Because in many instances thrombosis is bilateral, it is desirable to do a bilateral femoral ligation. Sears^{109, 110} states that all patients with thrombosis of the calf veins should have a proximal vein ligation as soon as the diagnosis is made. Thrombectomy has been advocated by L  wen⁶⁶ and Kulenkampf,⁶² the former extracting a thrombus through an opening in the femoral vein, the latter through the saphenous opening. Both attempt to save the deep venous system by suture of the vein wall. Lange⁶⁵ also advocates thrombectomy, but Freund³⁴ states that ligation should also be done. Allen and his co-workers² report an increasing incidence of femoral vein ligation at the Massachusetts General Hospital. In 1937, one femoral vein was tied; in 1938, none; in 1939, eight; in 1940, five; in 1941, fifty-five; and in 1942, 211. The right side was ligated in 46 per cent of the instances, and the left in 54 per cent. Sixty-one per cent of the operations were unilateral, and 39 per cent were bilateral. Whereas theoretically thrombectomy and suture of the vein seem desirable, and although the experimental work of Hintze and Zollenkopf⁴² appears to support the contention that these veins again function, we believe that not only is it unnecessary to attempt to save the vein, but that it is actually dangerous. Shackelford and Whitehill¹¹² report a case of multiple pulmonary emboli in which a cure was obtained by ligation of the left common iliac vein at its junction with the inferior vena cava. Although we originally contended that it was desirable to expose the vein above the site of involvement and ligate rather than attempt to aspirate the proximal portion of the clot, we now believe that the latter procedure is preferable. Exposure of the femoral vein in the upper part of the thigh can be performed with considerably less operative trauma than exposure of the external and common iliac veins through a retroperitoneal approach. The operation can be done under local analgesia, and can be done in the patient's bed, but is preferably done in the operat-

ing room. The patient is placed on the operating table with the trunk on a higher level than the thigh to increase the venous pressure in the femoral vessels. The femoral vein and its branches at its upper extremity are exposed. Care is taken not to manipulate the vein any more than is absolutely necessary, because a thrombus which is frequently difficult to detect before the vein is opened can be easily dislodged. Ligatures are carefully and loosely placed around the common femoral above the saphenous, around the profunda femoris, and around the superficial femoral. The long saphenous is doubly clamped close to the femoral and divided between the clamps. The distal end is ligated and the edges of the proximal end caught either with mosquito forceps or fine sutures. Into the proximal end a glass suction tube is introduced passing proximally into the femoral and external iliac veins, and gentle aspiration is maintained, in order that a contained thrombus can be aspirated. Aspiration is maintained until a free flow of blood occurs from the proximal portion, indicating an absence of clot between the opening in the saphenous vein and the inferior vena cava. Because of the elevation of the trunk and upper part of the body there will be an increase in the venous pressure and expulsion of the clot is favored. The femoral is then ligated above and below the saphenous opening. If there is free bleeding from the profunda femoris it need not be ligated, but if it also contains a thrombus it is to be ligated as well as the common femoral.

By the interruption of the involved vein above the site of the embolism in phlebothrombosis, one can prevent embolism from occurring, and in this way prevent infarction and fatality.

REFERENCES

1. Adams, Ralph, and Boehme, Earl J.: Prophylaxis Against Thrombosis, *Lahey Clin. Bull.* 3: 142, 1943.
2. Allen, Arthur, Linton, Robert R., and Donaldson, Gordon A.: Thrombosis and Embolism; Review of 202 Patients Treated by Femoral Vein Interruption, *Ann. Surg.* 118: 728, 1943.
3. Aschoff, Ludwig: Thrombosis, Lectures on Pathology, New York, 1924, Paul B. Hoeber, Inc.
4. Bahlis, C.: Aussprache über die Behandlung der Venenthrombose bei drohender oder bestehender Embolie, *Med. Klin.* 36: 216, 1940.
5. Barbour, H. C., and Hamilton, W. P.: Heat Regulation and Water Exchange; VII. Evidence That Cold Anhydremia Is Due to Loss of Fluid From Blood Stream, *Am. J. Physiol.* 73: 315, 1925.
6. Barker, N. W., Nygaard, K. K., Walters, W., and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism, *Proc. Staff Meet., Mayo Clin.* 15: 769, 1940, and 16: 1, 17, 33, 1941.
7. Barker, Nelson W.: The Use of Dicumarol in Surgery, *Minnesota Med.* 27: 102, 1944.
8. Barnes, A. R.: Pulmonary Embolism, *J. A. M. A.* 109: 1347, 1937.
9. Bauer, G.: A Venographic Study of Thromboembolic Problems, *Acta chir. Scandinav.* 84: 1, 1940.
10. Binschwager, quoted by Matas, R.: Postoperative Thrombosis and Pulmonary Embolism Before and After Lister, Donald C. Balfour Lecture in Surgery, *Univ. Toronto M. J.* 10: 1, 1932.
11. Birgus, J.: Verhuetung der Thrombosen und deren Roentgenbehandlung, *Ceskoslov. gynaek.* 18: 12, 1939.

12. Boldt, H. J.: The Management of Laparotomy Patients and Their Modified After Treatment. N. York M. J. 85: 145, 1907.
13. Bolognesi, G.: Untersuchungen über die Änderungen in der Blutviskosität infolge von chirurgischen Operationen, Zentralbl. f. Chir. 36: 1161, 1909.
14. Bumm, E.: Ueber die chirurgische Behandlung des Kindbelfiebers, Samml. zwangl. Abhandl. a. d. Geb. d. Frauenh. u. Geburtsh. 4: 1, 1902.
15. Bumm, E.: Zur operativen Behandlung der puerperalen Pyämie, Berlin, Klin. Wehnschr. 42: 829, 1905.
16. Bumm, E.: Ueber die operative Behandlung des Puerperalfiebers, Verhandl. d. deutsch. Gesellsch. f. Gynäk. 73: 105, 1909.
17. Bürger, Max, and Grauhan, Max: Über postoperativen Eiweißzerfall, Ztschr. f. d. ges. exper. Med. 27: 97, 1922.
18. Burke, M.: Thrombosis: A Medical Problem, Am. J. M. Sc. 196: 796, 1938.
19. Campeanu: Cited by Zava.¹⁷⁹
20. Collins, Conrad: Ligation of Vena Cava. (In press.)
21. deCourcy, J. L.: Venous Stasis as Cause of Postoperative Embolism: Its Prevention by Use of Reverse Fowler Position After Lower Abdominal Operations, Anesth. & Analg. 8: 342, 1929.
22. DeBakey, Michael, Burch, G. E., and Ochsner, Alton: Effect of Chemical Irritation of Venous Segment on Peripheral Pulse Volume, Proc. Soc. Exper. Biol. & Med. 41: 585, 1939.
23. deTakats, G., and Jesser, J. H.: Bronchial Factor in Pulmonary Embolism, SURGERY 12: 541, 1942.
24. Deuber, A.: Senkungsreaktion der Erythrozyten nach chirurgischen Operationen, Inaugural Dissertation, Basel, 1924, E. Birkhäuser et cie.
25. Donald, A., in discussion of Glynn, E. L.: Pulmonary Embolism and Primary Pulmonary Thrombosis, J. Obst. & Gynaec. Brit. Emp. 31: 526, 1924.
26. Drinker, C. K., Drinker, K. R., and Kreutzmann, H. A.: The Factors Concerned in the Appearance of Nucleated Red Blood Corpuscles in the Peripheral Blood; II. Influence of Procedures Designed to Increase the Rate of Blood Flow Through the Blood-Forming Organs—Hemorrhage and Infusion, J. Exper. Med. 27: 383, 1918.
27. Ewald, C.: Therapie der Thrombophlebitis und der Thromboembolie, Wien. klin. Wehnschr. 50: 377, 1917.
28. Faehraeus, R.: The Suspension-Stability of the Blood, Acta med. Scandinav. 55: 1, 1921.
29. Faure, J. L., in discussion, Morice, A.: Du traitement préventif des phlébites après hystérectomies pour fibromes par les autovaccines, Bull. et mém. Soc. nat. de chir. de Paris 53: 532, 1927.
30. Fischer: Cited by Friedländer.²
31. Frauendorfer: Cited by Müller-Meernach.⁷⁹
32. Friedländer, E.: Die Kompressionsbehandlung der Venenentzündung, Wien. klin. Wehnschr. 48: 791, 818, 1935.
33. Friedländer, E.: Anatomische Grundlagen zur Behandlung der Beckenvenen- und Femoralsthenose, Wien. klin. Wehnschr. 49: 1067, 1936.
34. Freund, W. A.: Ueber die Methoden und Indikationen der Totalexstirpation des Uterus, speziell in Bezug auf die Behandlung des Uteruskarzinome, Beitr. z. Geburtsh. u. Gynäk. 1: 343, 1898.
35. Hermann Dahl, J.: Postoperative Röntgenuntersuchungen; I. Diaphragmabewegungen und der postoperative venenstrom; II. Postoperative Lungenembolien, Acta chir. Scandinav. (Suppl.) 76: 1, 1935.
36. Frykholm, Ragnar: Pathogenesis and Mechanical Prophylaxis of Venous Thrombosis, Surg., Gynec. & Obst. 71: 307, 1940.
37. Gamble, H. A.: The Prevention of Postoperative Embolism and Phlebitis; With Description of Apparatus Employed, Am. J. Surg. 28: 92, 1935.
38. Hauser, quoted by Syller, R.: Thrombosen und Thrombosen bereitet nach Operationen, Beitr. z. klin. Chir. 145: 322, 1928-29.
39. Henderson, E. F.: Fatal Pulmonary Embolism; A Statistical Review, Arch. Surg. 15: 231, 1927.
40. Henle: Cited by Pool.⁹⁷
41. Heusser, H.: Postoperative Blutveränderungen und ihre Bedeutung fuer die Entstehung der Thrombose, Deutsche Ztschr. f. Chir. 210: 112, 1928.
42. Hintze, H., and Zollenkopf, H.: Experimentelle Untersuchungen über Behebung von Durchblutungsstörungen durch Thrombektomie, Zentralbl. f. Chir. 65: 2047, 1938.
- 42a. Homans, John: Circulatory Diseases of the Extremity, New York, 1939, The Macmillan Company.

43. Homans, John: Postoperative and Post-traumatic Thrombophlebitis of the Lower Limbs and Its Complications, *J. Internat. de Chir.* 3: 599, 1938.
44. Homans, J.: Thrombophlebitis in the Legs, *New England J. Med.* 218: 591, 1938.
45. Homans, J., and Zollinger, R.: Experimental Thrombophlebitis, *Arch. Surg.* 18: 992, 1929.
46. Huggins, R. R.: The Ligation or Excision of the Ovarian or Deep Pelvic Veins in the Treatment of Puerperal Thrombophlebitis, *J. A. M. A.* 59: 160, 1912.
47. Hunter, J.: Observations on the Inflammation of the Internal Coats of Veins, *Tr. Soc. Improve. Med. and Chir. Knowledge* 1: 18, 1793.
48. Hunter, W. C., Sneed, V. D., Robertson, T. D., and Snyder, G. A. C.: Thrombosis of the Deep Veins of the Leg: Its Clinical Significance as Exemplified in Three Hundred and Fifty-one Autopsies, *Arch. Int. Med.* 68: 1, 1911.
49. von Jaschke, R. T.: Neuere Erfahrungen im Kampf gegen die postoperative Thromboembolie, *Chirurg.* 9: 274, 1937.
50. Kaneko, S.: Experimentelle Thrombosenbildung durch Bakterieninfektion und intravenöse Einspritzung von Bakteriengift, *Arch. f. klin. Chir.* 197: 395, 1939.
51. Karsner, H. T.: Human Pathology, Philadelphia, 1926, J. B. Lippincott Company.
52. Kaufmann, E.: Lehrbuch der speziellen Pathologischen Anatomie, Vol. 1, Berlin, 1911, George Reimer.
53. Kenney, William E.: The Association of Carcinoma in the Body and Tail of the Pancreas With Multiple Venous Thrombi, *Surgery* 14: 600, 1943.
54. Kiban: Quoted by Heusser.⁴¹
55. Kirschner: Personal communication.
56. Kleinschmidt, O.: Die Nachbehandlung Laparatomierter, *Ergebn. d. Chir. u. Orthop.* 5: 432, 1913.
57. Knott, W.: Ueber die Verhütung von postoperativen Thrombosen und Embolien durch die Hochlagerung nach, H. H. Schmid, *Zentralbl. f. Gynäk.* 62: 679, 1938.
58. Koenig: Cited by Müller-Meernach.⁷⁹
59. Koester: Inaugural Dissertation, Bonn, 1870.
60. Koster, K. H.: Sympaticusblokade som Behandlung af Phlebitis, *Ugesk. f. læger* 103: 5, 1941.
61. Kreeke, A.: Ueber Vor- und Nachbehandlung bei Bauchoperationen, insbesondere über das frühzeitige Aufstehendlassen, München. med. Wehnschr. 57: 2037, 1910.
62. Kulenkampf, D.: Die Verhütung schwerer oder tödlicher Embolien durch Ausräumung der V. iliaca, *Zentralbl. f. Chir.* 62: 1258, 1933.
63. Kvale, cited by Ward, C. E., and Horton, B. T.: Postoperative Thrombophlebitis of Inferior Vena Cava in Child, *Proc. Staff Meet., Mayo Clin.* 12: 811, 1937.
64. Lambret, O., and Driessens, J.: Les modifications humerales post-opératives; Pathogénie—traitement; Recherches personnelles, *Echo méd. du Nord.* 9: 25, 1938.
65. Lange, E.: Beitrag zur operativen Behandlung der blanden Venenthrombose, *Zentralbl. f. Chir.* 65: 2422, 1938.
66. Lauen, A.: Arteriospasmus bei akuter massiver Thrombose der V. femoralis, *Zentralbl. f. Chir.* 61: 1681, 1934.
67. Lee, H.: The Surgical Treatment of Certain Cases of Acute Inflammation of the Veins, *Med. Times & Hosp. Gaz.* 1: 530, 1865.
68. Leriche, R.: Des moyens de réduire au minimum la maladie post-opératoire; de l'opération sous rayons infra-rouges, *Rev. de chir., Paris* 74: 99, 1936.
69. Leun, W.: Verhütung und Behandlung der Fernthrombosen mit elastischen Klebskompressionsverbänden, München. med. Wehnschr. 86: 1165, 1939.
70. Lockhart-Mummery, P.: Discussion on Post-operative Pulmonary Embolism, *Brit. M. J.* 2: 850, 1924.
71. Löhr, W.: Die Wert der Blutkörperchensenkungsgeschwindigkeit, als diagnostisches Hilfsmittel in der Chirurgie, *Zentralbl. f. Chir.* 48: 1267, 1921.
72. Löhr, W., and Löhr, H.: Ueber die Veränderung der Physikalisch-chemischen Struktur der Blutfüssigkeit bei beschleunigter Blutkörperchensenkung in Gefolge von Keizkörpertherapie chirurgischen Operationen und Erkrankungen, *Ztschr. f. d. ges. exper. Med.* 29: 139, 1922.
73. Mahler: Cited by Kulenkampf.⁶²

74. Martens, M.: Ueber Venenunterbindung bei thrombophlebitischer pyämie, *Verhandl. d. deutsch. Gesellsch. f. Chir.* 45: 246, 1921.
75. Meade, W. H., and Ochsner, A.: Spool Cotton as Suture Material, *J. A. M. A.* 113: 2230, 1939.
76. Miller, C. J.: The Present Status of Ligation or Excision of the Pelvic Veins in the Treatment of Septic Thrombophlebitis of Puerperal Origin, *J. A. M. A.* 59: 157, 1912.
77. Miller, C. J.: Ligation or Excision of the Pelvic Veins in the Treatment of Puerperal Pyaemia, *Surg., Gynec. & Obst.* 25: 431, 1917.
78. Morton, C. B., Shearburn, E. W., and Burger, R. E.: Synthetic Vitamin K and the Thrombosis of Veins Following Injury, *SURGERY* 14: 915, 1943.
79. Müller-Meernach, O.: Zur Frage der Prophylaxe der postoperativen Thrombosen und Embolie, *München. med. Wehnschr.* 84: 1880, 1936.
80. Neumann, R.: Ursprungszentrum und Entwicklungsformen der Bein—thrombose, *Virchows Arch. f. path. Anat.* 301: 708, 1938.
81. Ochsner, A.: Postoperative Treatment, *South. M. J.* 29: 53, 1936.
82. Ochsner, A., and DeBakey, M.: Thrombophlebitis and Phlebothrombosis, *South. Surgeon* 8: 269, 1939.
83. Ochsner, A., and DeBakey, M.: Thrombophlebitis; the Role of Vasospasm in the Production of the Clinical Manifestations, *J. A. M. A.* 114: 117, 1940.
84. Ochsner, A., and DeBakey, M.: Therapy of Phlebothrombosis and Thrombophlebitis, *Arch. Surg.* 40: 268, 1940.
85. Ochsner, A., and DeBakey, M.: The Role of Vasospasm in Thrombophlebitis and Its Treatment by Novocain Block of the Sympathetics, *Tri-State M. J.* 13: 2654, 1941.
86. Ochsner, A., and DeBakey, M.: Therapeutic Consideration of Thrombophlebitis and Phlebothrombosis, *New England J. Med.* 225: 207, 1941.
87. Ochsner, A., and DeBakey, M.: The Significance of Phlebothrombosis and Thrombophlebitis in Orthopedics, *J. Bone & Joint Surg.* 23: 788, 1941.
88. Ochsner, A., and DeBakey, M.: Rational Therapy of Thrombophlebitis, *New Orleans M. & S. J.* 94: 173, 1941.
89. Ochsner, A., DeBakey, M., and Schroeder, G.: The Significance of Phlebography in Thrombophlebitis and Phlebothrombosis, *J. A. M. A.* 123: 738, 1943.
90. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocain Block of Sympathetics; Technique of Injection, *SURGERY* 5: 491, 1939.
91. Ochsner, A., DeBakey, M., and Murray, S.: Pyogenic Abscess of the Liver; II. An Analysis of 47 Cases With Review of the Literature, *Am. J. Surg.* 40: 292, 1938; and Amebic Hepatic Abscess; An Analysis of 139 Cases With Review of the Literature, *J. Internat. de Chir.* 4: 1, 1939.
92. Ochsner, A., and DeBakey, M.: Thrombophlebitis and Phlebothrombosis, *Lewis' System of Surgery.* (In press.)
93. Ochsner, A., Gage, I. M., and Garside, E.: Intra-abdominal Postoperative Complications of Appendicitis, *Ann. Surg.* 91: 544, 1930.
94. Ophüls, W., and Dobson, L., cited by Rosenthal, S. R.: Thrombosis and Fatal Pulmonary Embolism, *Arch. Path.* 14: 215, 1932.
95. Patey, D. H.: Artificially Induced Thrombophlebitis With Suggested New Approach to Problem of Postoperative Pulmonary Embolism, *Surg., Gynec. & Obst.* 64: 1002, 1937.
96. Patey, D. H.: The Effect of Abdominal Operations on the Mechanism of Respiration; With Special Reference to Pulmonary Embolism and Massive Collapse of the Lungs, *Brit. J. Surg.* 17: 487, 1930.
97. Pool, E. H.: Systematic Exercises in Postoperative Treatment, *J. A. M. A.* 60: 1202, 1913.
98. Potts, W. J.: Pulmonary Embolism, *Ann. Surg.* 111: 554, 1940.
99. Prima, C.: Ueber Lokalisationsgrundlagen der Thrombose, *Zentralbl. f. Chir.* 65: 21, 1938.
100. Putnoky, J., and Farkas, K.: Vergleichende pathologisch-histologische Untersuchung des Herzmuskels bei 1009 Obduktionen, unter besonderer Beachtung der Fälle von Thrombosen und Embolien, *Virchows Arch. f. path. Anat.* 287: 400, 1932.
101. Reis, E.: Some Radical Changes in the After-treatment of Celiotomy Cases, *J. A. M. A.* 33: 454, 1899.
102. Richardson, M. H.: On Certain Unavoidable Calamities Following Surgical Operations, *Boston M. & S. J.* 151: 583, 1904.

103. Roessle, R.: Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen, *Virchows Arch. f. path. Anat.* 300: 180, 1937.
104. Rokitsansky, cited by Benda: Venen, *Handbuch der speziellen pathologischen Anatomie Henke u. Lubarsch*, Vol. 2, Berlin, 1924, Julius Springer.
105. Schmid, H. H., discussion of Dick's article: *Zentralbl. f. Chir.* 65: 1937, 1938.
106. Schmid, H. H.: Verhütung von postoperativen Thrombosen und Embolien, *Zentralbl. f. Gynäk.* 61: 37, 1937.
107. Schmiedt, W.: Beitrag zur Thrombosebehandlung durch Beckenentlastung, *Zentralbl. f. Chir.* 65: 2442, 1938.
108. Schollenberg, cited by Krotoski, J.: Zur Venenunterbindung bzw.—exstirpation bei der puerperalen Allgemeininfektion von chirurgischen Standpunkt, *Chirurg.* 9: 425, 1937.
109. Sears, J. B.: Embolism From Saphenous Thrombophlebitis and Its Prophylaxis, *New England J. Med.* 212: 874, 1935.
110. Sears, J. B.: Experience With Femoral-vein Ligation for Prophylaxis of Postoperative Pulmonary Embolism, *New England J. Med.* 224: 108, 1941.
111. vonSeemen, Hans: Operation und Gewebeschonung; II. Beziehungen Zwischen Operationswunde und Entstehung, Vermeidung und Bekaempfung der mittelbaren Operationschädigungen (spontane Venenthrombose und Pneumonia), *Deutsche Ztschr. f. Chir.* 223: 85, 1930.
112. Schackelford, R. R., and Whitehill, W.: Successful Ligation of the Left Common Iliac Vein for Thrombophlebitis Complicated by Pulmonary Emboli, *Bull. Johns Hopkins Hosp.* 73: 307, 1943.
113. Smith, L. A., and Allen, E. V.: Vascular Clinics; Studies on the Rate of Venous Blood Flow; Physiologic Studies and Relation to Postoperative Venous Thrombosis and Pulmonary Embolism, *Proc. Staff Meet., Mayo Clin.* 16: 53, 1941.
114. Snell, A. N.: Relation of Obesity to Fatal Postoperative Pulmonary Embolism, *Arch. Surg.* 15: 237, 1927.
115. Sproul, E. E.: Carcinoma and Venous Thrombosis; The Frequency of Association of Carcinoma in the Body or Tail of the Pancreas With Multiple Venous Thrombosis, *Am. J. Cancer* 34: 506, 1938.
116. Starlinger, W., and Samentik, S.: Ueber die Entstehungsbedingungen der spontanen Venenthrombose, *Klin. Wehnschr.* 6: 1269, 1927.
117. Starlinger, W., and Winands, E.: Ueber das Vertheilungsverhaeltnis der zirkulierenden Eiweisskoerper im Verlaufe krankhafter Zustaeude, *Ztschr. f. d. ges. exper. Med.* 60: 208, 1928.
118. Stich: Annual Session of the German Surgical Society, *J. A. M. A.* 105: 525, 1935.
119. Sulger, quoted by Matas, R.: Postoperative Thrombosis and Pulmonary Embolism Before and After Lister, Donald C. Balfour Lecture in Surgery, *Univ. Toronto Med. J.* 10: 1, 1932.
120. Trendelenburg, F.: Ueber die chirurgische Behandlung der puerperalen Pyämie, *München. med. Wehnschr.* 49: 513, 1902.
121. Trousseau, A.: Cited by Sproul.¹¹⁵
122. Viereck: Die Unterbindung der Vena jugularis bei der Thrombose des sinus transversus, *Verhandl. d. deutsch. otol. Gesellsch., Jena* 9: 77, 1900.
123. Victor, J. A.: Clinical Considerations of Thrombosis and Embolism, *Ann. Surg.* 82: 193, 1925.
124. Wangenstein, O.: The Therapeutic Problem in Bowel Obstruction, Springfield, Ill., 1937, Charles C Thomas, Publisher.
125. Weinstein, B.: Personal Communication.
126. Wildegans, H.: Zur Entstehung der Venenthrombose, *Arch. f. klin. Chir. (Kongrassbericht)* 148: 592, 1927.
127. Wilson, L. B.: Fatal Post-operative Embolism, *Ann. Surg.* 56: 809, 1912.
128. Zarubin, cited by Matas, R.: On the So-called Primary Thrombosis of the Axillary Vein Caused by Strain; Report of a Case With Comments on Diagnosis, Pathogeny and Treatment of This Lesion in Its Medicolegal Relations, *Am. J. Surg.* 24: 642, 1934.
129. Zaufal, H.: Sinusthrombose, *Prag. med. Wehnschr.* 5: 517, 1880.
130. Zava, L.: Sui vantaggi del levar precoce delgi operati, *Policlinico (sez. prat.)* 47: 865, 1940.
131. Zink, cited by Aschoff, L.: Ueber Thrombose und Embolie, *Wien. klin. Wehnschr.* 51: 1277, 1938.

DISASTER FOLLOWING FEMORAL VEIN LIGATION FOR THROMBOPHLEBITIS; RELIEF BY FASCIOTOMY; CLINICAL CASE OF RENAL IMPAIRMENT FOLLOWING CRUSH INJURY

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DESPITE the contributions of Ochsner, Fine, Allen, Waugh, and others, there is as yet no unanimity of opinion among surgeons as to the most adequate type of therapy to employ in postoperative thrombophlebitis. The results published by Fine and Frank indicate that most such cases, in which the presence of the disease has been demonstrated by venograms, are relieved, both of local evidences of the disease and of the danger of embolism, by high ligation of the veins above the involved area. Allen and his associates found no deleterious effects to follow such high ligation, as ligation of the femoral vein above the fossa ovalis, and recommended free use of such ligation in cases of postoperative thrombophlebitis.

In the past few months one patient so treated at the University of Minnesota Hospitals has developed serious complications following high ligation of the femoral vein, which should be brought to general attention.

CASE REPORT

D. M. (Hospital No. 739518), a 59-year-old janitor, came to the University of Minnesota outpatient department, Dec. 18, 1943, complaining of a tender mass in the left groin. The mass had developed in the previous three months, during which time he had been wearing a truss for a right inguinal hernia. Questioning showed that at the age of 16 he had had rheumatism, during which his elbows had been swollen and painful. He had had a left inguinal hernioplasty in 1930, pleurisy about 1935, backache "all his life," and had been an excessive user of alcohol.

Physical examination showed a small indirect inguinal hernia on the right side, kept well reduced by a truss. There was a scar from the old hernioplasty on the left side. Just below this scar was an egg-shaped mass 7 by 3 cm., hard, fixed, and tender. The left testis was atrophic.

The man was sent to the outpatient tumor clinic because the marked induration and fixation of the mass suggested a neoplastic process rather than a hernia. He was admitted to the hospital, December 21, for excision biopsy of the mass. Exploration, December 24, under combined spinal and cyclopropane anesthesia revealed a femoral hernia containing incarcerated, necrotic omentum. The inguinal ligament was divided by the surgeon to facilitate removal of the sac, and a modified McVay-Harkins type of repair was made, using No. 3 Champion silk suture. Sulfathiazole was implanted in the course of the repair.

In the first three days postoperatively the patient had a temperature as high as 101° F., but following the fourth day remained afebrile until January 6, thirteen days after surgery. January 1, however, eight days after surgery, he presented a positive Homans' sign on the left side, and tenderness and local heat in the left

calf. One per cent procaine sympathetic block of the left first and second lumbar levels at once, and of the first, second, and third levels the next day, relieved the patient entirely.

January 5, twelve days after surgery, swelling and tenderness appeared around the wound, and sulfathiazole therapy was begun, 1 Gm. every six hours, by mouth. January 7, a small amount of purulent exudate was evacuated from the wound, and the temperature commenced to rise, reaching 105.4° F. on January 9, sixteen days after surgery, when the sulfonamide was discontinued because of the feeling that this represented drug fever. (See Fig. 1.) The temperature dropped almost to normal in the ensuing three days. The wound had apparently healed by January 12. Nausea and vomiting, January 10 and 11, were attributed to the sulfonamide.

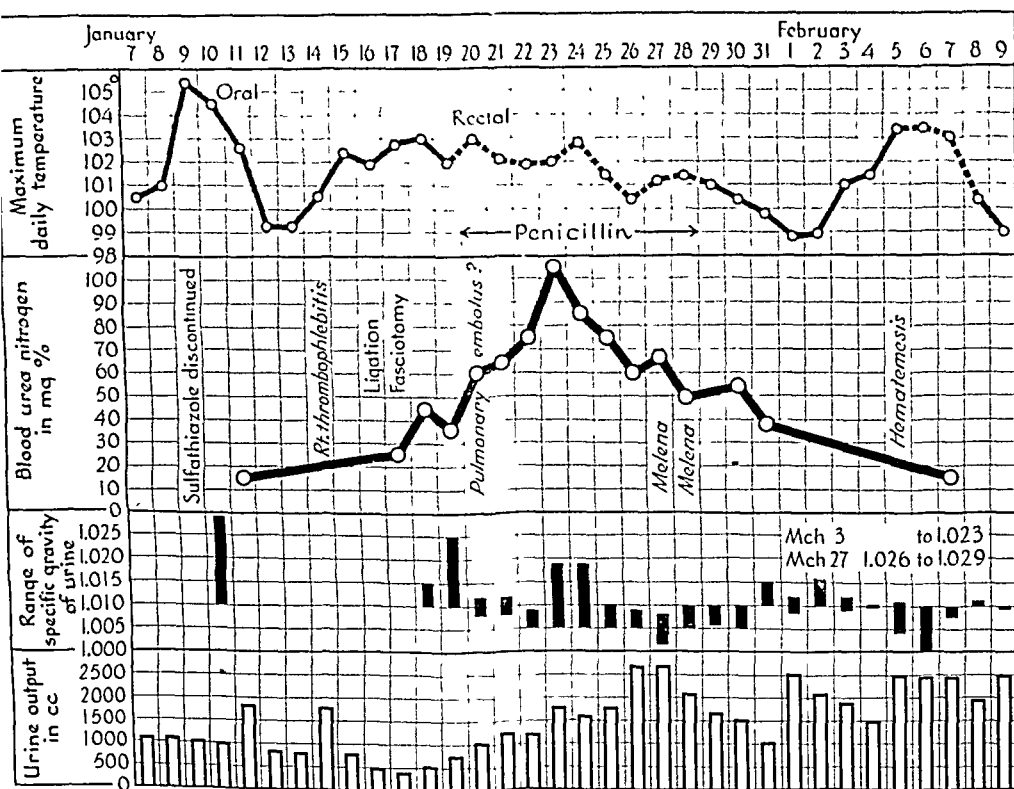


Fig. 1.—Variations in blood urea nitrogen level, urinary output, and urinary specific gravity ranges in the period following relief of engorgement of the right leg by fasciotomy.

The patient was to have been dismissed January 14, twenty-one days after the hernioplasty, but on the morning of this day he developed swelling, tenderness, and a positive Homans' sign in the right lower leg. Lumbar sympathetic block failed to give relief, either January 14 or when repeated January 15.

January 16 the patient looked sicker than at any time earlier (see Fig. 1). The circumference of the right calf (measured 15 cm. below the lower margin of the patella) was 38.5 cm. as compared with 37 cm. a day earlier and 30 cm. a week earlier. At noon the right leg was pinker and definitely warmer than the left, and there were numerous engorged veins, particularly below the knee. A firm thrombus could be palpated extending from the knee upward to a point 12 to 15 cm. below the inguinal ligament in or overlying Hunter's canal.

Three courses of therapy were considered: (1) more procaine injections, which seemed inadvisable because of earlier experience with fatal embolus in cases with little inflammatory reaction; (2) anticoagulant therapy, not adopted because the process seemed too rapid for dicumarol and because labor trouble at the hospital had made help too inadequate to embark on the use of heparin; (3) the ligation of the femoral vein above the saphenous opening.

At 3:00 P.M., January 16, removal of the junction of the right femoral and saphenous veins was completed under 1 per cent procaine block anesthesia. The segment removed contained both liquid blood and thrombus. At the end of this resection a small spurting vessel was found between the artery and the vein distally. It spurted a colorless clear liquid, not blood, and it was also ligated.

Upon removal of the drapes, the whole leg was seen to be engorged and deeply cyanotic, and the patient complained of pain in the leg and of numbness of the sole of the foot. The calf now measured 39.8 cm. in circumference, and the tightness of the skin soon became marked enough to render the surface shiny. The pulse on the dorsum of the left foot could be easily felt, but the right dorsalis pedis pulse was very feeble, though definitely present.

Procained lumbar sympathetic block was employed at once, without more than minimal improvement, and the temperature of the right leg began gradually to fall.

About 7:00 P.M., January 16, the blood pressure dropped sharply to 40/0. Administration of 1100 c.c. of plasma and 500 c.c. of whole blood returned the pressure to normal levels. This amount was repeated the following day. At 9:00 P.M., January 16, the measurements of the two legs were as indicated in Table I.

TABLE I

CIRCUMFERENCES OF LEGS SIX HOURS AFTER RIGHT FEMORAL VEIN LIGATION

	RIGHT	LEFT
Thigh (15 cm. above top of patella)	60 cm.	44 cm.
Knee	33 cm.	36 cm.
Calf (15 cm. below bottom of patella)	40 cm.	30 cm.
Ankle	24 cm.	20 cm.
Roughly calculated volume	9½ liters	6½ liters

The loss of fluid into the right leg was calculated to be at least 3 liters. The patient was observed in steep Trendelenburg position overnight.

Skin temperatures were observed by the use of a thermocouple. At 9:00 P.M. there was no consistent difference in the two legs, but by the following noon the temperatures in the right leg were definitely dropping. Tissue tensions were also determined late in the evening of January 16.

TABLE II

SUBCUTANEOUS TISSUE TENSION DETERMINATIONS EIGHT HOURS AFTER RIGHT FEMORAL VEIN LIGATION

	RIGHT (CM. OF WATER)	LEFT (CM. OF WATER)
Thigh	24	4.5
Knee	37	16.5
Calf	19.5	20
Ankle	43	1

The temperature of the right leg continued to fall, the tension of the skin increased slowly, and the leg became more blue and black in color. Reanastomosis of the vein did not seem feasible, and division of the deep fascia was therefore performed at 6:00 P.M., January 17, after a good spinal anesthesia had failed to bring improvement. Fasciotomy was suggested by Dr. O. H. Wangenstein in line with

the experimental findings of Jepson. Longitudinal incisions were made extending from about 5 cm. below the knee joint to about 10 cm. above the ankle medially and laterally and from 5 cm. above the knee joint to a point 10 cm. below the groin medially, and to a corresponding level on the lateral side of the leg. The wound of the femoral ligation was re-explored at this time. There had been no hemorrhage there, and the wound was found clean and dry. The femoral artery could be felt pulsating normally in the depth of this wound, but in the course of the medial fasciotomy a finger was placed beneath the sartorius muscle, and no pulsation could be felt at this level. The muscles were very edematous, and bulged hugely from the fasciotomy incisions at all points. In the lateral thigh incision there was arterial bleeding; this was found nowhere else. Sulfanilamide powder (10 Gm.) was packed into the wounds with petrolatum packing. Following fasciotomy, and while the patient was still on the table, the leg rapidly became warmer below the knee.

January 20, three days after fasciotomy, the patient complained of chest pain on the left side, and physical signs suggested consolidation. Because of persistent fever and a shaking chill, penicillin was started (10,000 Oxford units every three hours by intramuscular injection). It was administered thus until January 28. On January 24, a roentgen film of the chest indicated an infarction of the left middle lobe. The temperature gradually dropped under penicillin therapy.

January 28, abdominal cramps, distention, vomiting, and melena appeared, confirming the fear that mesenteric venous occlusion might complicate the picture. For the next week vomiting persisted, often bloody in character, and the patient remained critically ill. Thereafter, improvement in the gastrointestinal functions gradually took place.

By March 1, the patient presented clean, granulating fasciotomy wounds except for some necrosis in the lower medial incision. Motor power in this extremity had been lost completely below the knee, and sensation was present, but impaired. Ability to flex and extend the knee was partial.

On March 2, the patient developed pain in the *left* calf, with a positive Homans' sign, and tenderness in the calf and along the course of Hunter's canal. There were petechiae overlying Hunter's canal, and there was swelling of the entire extremity. The leg was cold except for a small area of local heat overlying the femoral vein. Following three days of roentgen therapy, the pain seemed to diminish slightly, but the swelling became more marked, and consequently heparinization was undertaken, using the continuous intravenous infusion method in such fashion as to maintain a capillary tube-method clotting time of about twenty-five minutes. Dicumarol* was started simultaneously in sufficient dosage to keep the prothrombin time ten seconds above the control level. Heparin was discontinued, March 11, because the prothrombin time had been adequately prolonged, but dicumarol was given until the end of the month.

Under this therapy, all evidences of thrombophlebitis disappeared in one week, and have not recurred.

The patient was kept in the hospital until early July for physiotherapy and because of a polyarthritis which now has disappeared. At the time of dismissal there was a small unhealed area at the lower end of the lower medial fasciotomy incision only, and all evidences of thrombophlebitis had been absent for three months. Function has not yet returned to the muscles of the right lower leg, but the patient is able to stand and to bear some weight (Fig. 2).†

*Supplied to Dr. C. J. Watson through courtesy of Abbott Laboratories. The author is indebted to Dr. Watson for permission to use the drug in this case.

†This patient returned to the hospital in December, 1944, with what appeared to be recurrent thrombophlebitis of the right leg. He has had one attack of thrombophlebitis since July, 1944, in the left leg also. Therapy with dicumarol has been effective each time.

Recent detailed questioning has shown that the patient had a mild attack of thrombophlebitis in 1942.

It is thought that interference with venous return developed in this patient by the phlebitic involvement of those collateral veins about the upper end of the femur which ordinarily serve as a pathway for return blood flow after high femoral and saphenous vein ligation. Salvage of the leg by fasciotomy a day later must have been possible because of the opening of additional collateral channels.

Of particular interest in this patient is the evidence of renal damage apparent in Fig. 1. Following fasciotomy, the patient developed uremia despite a good urinary output, and there appeared to be a simultaneous loss in the ability of the kidneys to concentrate the urine. The damage suggests that which has been described by Blalock as following prolonged use of the tourniquet experimentally. It was temporary in this instance, as the blood urea nitrogen level fell, and the ability of the kidneys to concentrate returned in about six weeks.



Fig. 2.—Photograph of patient six months after femoral ligation. The legs have returned to normal size, and the patient can bear some weight on the right foot.

COMMENT AND CONCLUSION

The possibilities of exploration of the collateral venous return in the upper thigh by venograms in the presence of thrombophlebitis are being explored. There is some tendency in this clinic in the meantime toward

conservatism in femoral ligation in those cases in which more than one venous bed has been involved. Femoral vein ligation, use of anticoagulants, strict conservatism, sympathetic procaine block, and roentgen therapy are all being used in an effort to evaluate the indications for each, but this evaluation has not as yet been accomplished.

This case is presented as a warning that indiscriminate use of femoral vein ligation above the fossa ovalis for symptoms of thrombophlebitis is not devoid of danger.*

REFERENCES

1. Allen, A. W., Linton, R. R., and Donaldson, G. A.: Thrombosis and Embolism, *Ann. Surg.* 118: 728, 1943.
2. Barker, N. W., Allen, E. W., and Waugh, J. M.: The Use of Dicoumarol [3,3'-methylene-bis-(4-hydroxycoumarin)] in the Prevention of Postoperative Thrombophlebitis and Pulmonary Embolism, *Proc. Staff Meet., Mayo Clin.* 18: 102, 1943.
3. Blalock, Alfred: A Consideration of the Present Status of the Shock Problem, *SURGERY* 14: 487, 1943.
4. Fine, J., and Frank, H. A.: Recent Experiences With Thrombophlebitis of the Lower Extremity and Pulmonary Embolism, *Ann. Surg.* 116: 574, 1942.
5. Harkins, H. N., Szilagyi, D. E., Brush, B. E., and Williams, R.: Clinical Experiences With McVay Herniotomy; 131 Personal Cases, *SURGERY* 12: 364, 1942.
6. Jepson, Paul N.: Ischaemic Contracture: Experimental Study, *Ann. Surg.* 84: 785, 1926.
7. Ochsner, Alton: The Treatment of Thrombophlebitis by Novocaine Block of Sympathetics, *SURGERY* 5: 491, 1939.
8. Pendergrass, E. P., and Hodes, P. J.: Roentgen Irradiation in the Treatment of Inflammations, *Am. J. Roentgenol.* 45: 74, 1941.

*In the recent past another instance of inadequate collateral venous return has been encountered. The patient is a 19-year-old girl who has had a total colectomy for chronic ulcerative colitis and who has had repeated attacks of superficial and deep thrombophlebitis bilaterally. Thrombophlebitis returned one year after right saphenous ligation for superficial disease, and right lumbar sympathectomy early in 1944 relieved the symptoms of the disease in that leg until December, 1944, when right deep thrombophlebitis again developed. A venogram showed a single narrow vein draining the extremity. Under pentothal anesthesia a loose catgut strand was placed under the femoral vein. Venous pressure at the ankle was 7 cm. of blood without compression of the femoral vein, but with occlusion by means of the strand the venous pressure at the ankle rose to 38 cm. of blood in less than two minutes. The entire skin of the extremity assumed a dusky, blotchy appearance during compression of the vein. Ligation was not done.

It is suggested that venous pressure measurements be made at the ankle during compression of the femoral vein under direct vision prior to ligation in those patients in whom there have been repeated or widespread thrombophlebitic episodes.

THE SENSATION OF GAS STOPPAGE DURING THE ONSET OF ACUTE APPENDICITIS

WITH ILLUSTRATIVE CASES

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IN PRACTICE the surgeon delays his diagnosis of acute appendicitis until pain localizes. The appendix may perforate while the surgeon waits.

Precise study has revealed that the onset of acute appendicitis may be made the foundation of accurate diagnosis even prior to localization because of a symptom complex, the gas stoppage sensation.¹ It is the purpose of this paper to illustrate the gas stoppage sensation as a basis for diagnosis.

THE ACCEPTED VIEW OF ONSET

By onset is meant those first hours of vague abdominal discomfort prior to localization. So vague may be this discomfort as to cause some patients to forget or to disregard anything before the pain in the right iliac fossa. Therefore "it is well in taking the history of any acute abdominal condition to focus the patient's mind on the beginning of the attack," as Richardson² wrote in 1930.

Homans³ in 1940 described the onset of acute appendicitis in a manner little short of pathognomonic. He wrote as follows:

A very typical attack in a young adult is ushered in by pain, which appears to be due, at an early stage at least, to overdistension of the appendix. Thus it partakes of the nature of a colic—a sustained colic, not an intermittent one, such as is caused by a violent spasm of the appendix itself. Moreover, like many other acute pains arising within the peritoneal cavity, it can seldom be exactly located but is referred to the center of the abdomen, the region of the umbilicus, or the epigastrium. It varies from an almost unbearable ache to a feeling of nagging discomfort, but is usually severe and associated with nausea, perhaps vomiting. Very rarely is it relieved temporarily by the passage of gas or a movement of the bowels. After several or many hours it subsides, to be exchanged for a feeling of soreness in the right iliac fossa, that is, in the region of the appendix itself.

THE GAS STOPPAGE SENSATION

Note the essential elements of Homans' description: a sustained colic, vaguely located in the midline (and associated with nausea and vomit-

¹The author's father, E. L. Keyes, M.D., of New York, helped in preparing this paper.

Received for publication, July 12, 1944.

ing), rarely relieved temporarily by the passage of gas or a movement of the bowels.

If the phrase about nausea and vomiting in parenthesis is omitted, an almost perfect description of the sensation of gas stoppage remains, though the emphasis is not where it should be. The sensation of gas stoppage merits the name because it is always a desire to pass gas downward rather than up and is characteristically relieved little, if at all, by whatever gas or feces does pass. It is a subjective sensation—a symptom, not a sign. Fitz⁴ long ago recorded a characteristic of gas stoppage when he noted that “a cathartic or laxative may be demanded by the patient.”

Homans is influenced by the formula made traditional by Murphy⁵ to write that the “discomfort . . . is associated with nausea, perhaps vomiting.” What Murphy actually stressed is the order of symptoms, and not their association. He made this clear by writing “the order is all-important in making a diagnosis: First pain . . . referred at first usually to the epigastrium . . . gradually changing to the right iliac fossa or to the location of the inflamed appendix. Second, nausea and vomiting.”

Nausea and vomiting, however, do not always occur. (See Table I.) The true characteristic of the onset, prior to localization, is the sensation of gas stoppage, persisting whether or not the bowels move or gas is passed by rectum.

Gas stoppage is usually present at onset regardless of whether subsequent localization is “typical,” “atypical,” or absent entirely.

It is also essential to note that the gas stoppage sensation characterizes the onset of acute appendicitis and only the onset. When an acute attack begins with the “pain of localization” there is no sensation of gas stoppage. Such cases are relatively uncommon.

TABLE I
THE GAS STOPPAGE SENSATION IN TEN PATIENTS WITH APPENDICITIS

CASE	THE ONSET					LOCALIZATION	PATHOLOGY
	COULD PATIENT PASS BY RECTUM		NAUSEA?	VOMIT- ING?	DURATION OF ONSET (IN HR.)		
	GAS?	FE- CES?					
1	No	Yes	Yes	Yes	19	Typical (?)	Acute
2	No	Yes	Yes	No	17	Typical	Acute
3	Yes	Yes	No	No	7	Typical	Ruptured
4	No	No	No	Yes	12	Atypical	Ruptured
5	No	No	No	No	1½	Typical	Subacute
6	No	No	No	No	48	None	Ruptured
7	No	No	Yes	No	28	None	Ruptured
8	Yes	Yes	No	Yes	24	None	Acute
9	No	No	Yes	No	30	Atypical (?)	Subacute
10	No	No			24	Typical	Subacute

If the patient does not mention spontaneously the sensation, and few patients do, there are two, sometimes three, questions, necessary to elicit the information.

1. "At onset, did you feel as if gas or something were stopped up inside?"

To this question the patient with gas stoppage usually answers Yes.

2. "At onset, did you feel that passing gas by rectum or moving the bowels would relieve the feeling?"

To this the patient answers Yes.

3. (For patients able to pass gas or to defecate during onset.) "Was the feeling completely relieved by passing gas by rectum or by a movement of the bowels?"

To this the patient answers No.

EXAMPLES OF THE GAS STOPPAGE SENSATION IN PATIENTS

CASE 1.—A 22-year-old medical student, not yet studying surgery, reported because of abdominal discomfort. The onset was gradual, about 2 P.M. the day before, March 19, 1944. Discomfort was dull and generalized in the lower abdomen, and to the patient it felt as though gas was stopped up inside him. He felt if he could pass gas by rectum he might obtain some relief, but he could pass no gas. The discomfort increased and moved upward about the umbilicus. Lying quiet helped it; eating increased it. The bowels moved without any gas passage about 9 P.M., but the movement gave no relief. There was nausea and about midnight the patient vomited three or four times. He felt better about 9 A.M. when the pain localized somewhat in the right iliac fossa, and at which time he was first seen. He took no laxative. The temperature was 98.4° F., the pulse 78. He looked somewhat sick. When first examined there was slight tenderness one inch to the right and below McBurney's point, and slight tenderness by rectum. All physical signs disappeared completely after he lay in bed about one hour and other observers then seeing him found him asymptomatic and without abdominal or rectal signs. The leucocytes were 10,850 at 10 A.M., with 1 per cent eosinophiles, 10 per cent stabs, 75 per cent segments, 8 per cent lymphocytes, and 6 per cent monocytes.

The diagnosis by two of us familiar with gas stoppage sensation was subacute appendicitis; the diagnosis by two others was uncertain. At operation a swollen, red appendix was removed. It was constricted at the base with distal swelling, clinically acute. The histologic diagnosis was acute appendicitis.

This patient had had a previous attack which he said was similar and for which he consulted a fellow staff member on July 7, 1943. Following is his note: "Vague onset yesterday afternoon with pain in lower right quadrant. Nausea and vomiting this morning, no diarrhea. Pain, however, has not been acute today. He states he feels better now. The belly is flat and not particularly tender. Deep pressure over the cecum elicits only slight tenderness. Leucocytes 14,600, stabs 3 per cent, segments 88 per cent, lymphocytes 8 per cent. Impression: Enteritis, although mild retrocecal appendicitis cannot be excluded. Recommend bed rest and liquid diet."

Comments on Case 1.—An intelligent patient told a clear story spontaneously. He answered the three questions, Yes, Yes, No. Localization was indefinite. Operation revealed acute appendicitis.

CASE 2.—A 24-year-old medical student reported complaining of pain in the belly which began June 1, 1944, at about 9 A.M. Following are the patient's words copied

verbatim as he talked with me at 3 P.M., June 2, before I operated on him, names and irrelevant questions being omitted.

"Yesterday morning at 8 o'clock I had a normal bowel movement following breakfast. At 9 o'clock I first noticed mild cramps in the upper epigastrium. They didn't interfere enough with classes so I kept on with my work until 11:30 A.M. Cramps were still mild at that time. Then I ate chili and drank a glass of milk, and went to Clinical Pathological Conference. I remained there five or ten minutes; the cramps became much worse. Quite a few fellows smoke in there; I felt nauseated and went home. At about 2 P.M. I had a bowel movement, the same as the one I had had this morning. I thought the bowel movement would clear everything up, but it didn't seem to make any difference, so I went back to bed and slept till 6 P.M. I didn't feel like eating any supper so I came to see Dr. ——— who said I had nonspecific enteritis. He gave me some papaverine tablets. They didn't help. About 8 or 9 P.M. I felt some distention. I felt that if I could pass a lot of flatus or belch, it would help, but I couldn't. I tried to pass flatus or to have a bowel movement but I couldn't. I slept from 11 P.M. to 2 A.M., then I felt tenderness in the right lower quadrant on palpation so I saw another doctor, who said I had nonspecific enteritis and gave me nembutal. I slept from 4 A.M. to 8 A.M. and on waking felt pain in the right lower quadrant. I took a glass of milk and poached egg on toast, then slept from 9 A.M. until noon. I noticed that the cramps were not relieved and everything was about the same, with the same amount of tenderness in the right lower quadrant. In the last half hour there has been more tenderness in the right lower quadrant."

I asked him the following questions referring to the gas stoppage sensation.

"At onset, did you feel as if gas or something was stopped up inside?"

"No, not then; but I did feel that way around eight or nine o'clock last night." (Eleven or twelve hours after onset.)

"At onset, did you feel as if you might have obtained relief by defecating or by passing gas per rectum?"

"No, not then, but around eight or nine o'clock last night I felt if I could pass flatus it would help and I made three unsuccessful attempts at stool."

Examination showed a temperature of 99.8° F.; pulse 90; leucocytes 16,300, with eosinophiles 2 per cent, stabs 8 per cent, segments 68 per cent, lymphocytes 15 per cent, and monocytes 5 per cent. The patient looked sick; the face was flushed, the pupils wide. He lay on his back with the thighs flexed. He looked dehydrated, although the tongue was moist, not furred, and the breath sweet. The abdomen was distended, with hyperesthesia in the right lower quadrant and tenderness and spasm all over the right lower quadrant, most marked about one inch below McBurney's point. Rebound tenderness. No retraction of the right testicle. Tenderness on right side by rectal examination. Diagnosis: acute appendicitis.

Fluids were given intravenously preparatory to operation but, during the few hours between admission and arrival in the operating room, the temperature suddenly rose to over 104° F. (anesthetist's report) and the pulse to 132. The patient looked poorly; consequently he was sent back to his room and plasma and sulfadiazine were administered, with opiates, etc., postponing operation over twelve hours. Operation, finally performed by me about forty-two hours after onset, revealed a gangrenous appendix ruptured in two places by a large ovoid, soft olive-colored fecalith one centimeter in diameter. About the appendix was a local accumulation of pus and there was marked increase of dirty fluid in the peritoneum, suggesting generalized peritonitis. Appendectomy. Histologically acute appendicitis.

Comments on Case 2.—The gas stoppage was established by 2 P.M., marked by evening, yet the diagnosis was missed twice and the appendix

was ruptured when removed. A dangerous illness might have been spared the patient by early diagnosis.

CASE 3.—A 25-year-old medical student complained of abdominal pain, which had begun suddenly the night before, as a sharp epigastric pain. In a few minutes it had become severe and griping and ten minutes later spread over the upper abdomen, as far down as the umbilicus. He thought of something to bring the gas up but this feeling, he said, was not nausea. A few minutes later he passed a lot of gas and a large soft stool. This relieved him somewhat and then the discomfort was dull and diffuse, a soreness all over the abdomen. He felt shaky and broke into a cold sweat. He took hot tea with some temporary relief. An hour after onset he passed a large fluid stool, although no laxative had been taken. The movement helped somewhat, but he passed no gas. He slept restlessly.

I questioned him as follows: "Try to describe the feeling at onset."

"I can't describe it."

"At onset, did you feel as though gas or something was stopped up inside?"

"Yes."

"At onset, did it feel to you as if passing gas by rectum or moving the bowels would relieve the feeling?"

"Yes."

Localization of pain began about 6 A.M., in the right iliac fossa. He ate no breakfast. He lay flat on his back for relief.

There had been many previous attacks, notably one six months before, of two hours' duration. At that time he had an urge to defecate and made two efforts; the first resulted in a bowel movement, the second did not. But he could not answer the three questions as to these former attacks.

He looked somewhat sick. The tongue was slightly furred. A point of maximum tenderness was found halfway between the right anterior superior spine and the umbilicus with referred pain, no rebound tenderness, and no tenderness by rectum. Temperature was 98.6° F.; pulse 88; urine, 1 plus albumin; leucocytes 13,200, with eosinophiles 1 per cent, stabs 16 per cent, polymorphonuclears 78 per cent.

Diagnosis: acute appendicitis. An acutely inflamed appendix was removed. Histologically acute appendicitis.

Comments on Case 3.—This was the most enlightening history of the lot. A medical student called his initial symptom pain, griping, dull soreness, then "I can't describe it." This real discrepancy in the story of an unusually intelligent young man shows how vague the discomfort was to him and the three questions crystallized his notions.

And to confuse the issue still further, to one of the surgeons, asking the three questions without reference to any particular time, the patient, thinking he referred to the present, answered, "No" to all of them for, localization having taken place, the gas sensation had disappeared.

When the questions were repeated with strict reference to onset he gave the answers, Yes, Yes, No.

CASE 4.—A 51-year-old hospital stretcher-bearer complained of cramps in the stomach and vomiting. Vague onset at about 2:30 P.M. caused him to take an enema, but he then disregarded the pain. Suddenly that evening at 6:30 P.M., prior to admission, cramps became severe. In his own words, there were "cramps in my stomach right after I'd eaten supper and took a ride downtown. I felt them coming on and the jar of the bus would affect me so that I wanted to get off. I felt

if I could get my bowels to move it would go away. I got off the bus, went into a tavern, and sat on the toilet about fifteen minutes. The bowels did not move and I couldn't pass any gas or anything. (At this time he vomited once.) Then I came out and I was still having cramps. All this time the cramps were in the lower part, way down over my bladder. I went to a drugstore and got some red drops. I took a few drops in water and it seemed to relieve me some. Then I went out in the park and sat down on a bench and the cramps came back again. Then I came home and went to bed and took some more red drops. I kept going to the toilet, thinking my bowels would move. Finally I took two laxative tablets about 10:30 P.M. About midnight the bowels seemed to work gradually. Their action would relieve for a bit, just for a few minutes, but I was never really comfortable and I never slept more than five minutes all night. I was up and down all the time (and vomited seven or eight times). Toward morning the pain went down to my scrotum and I was in for it. So I went to the doctor."

He answered the three questions, Yes, Yes, No.

The patient appeared very sick and was holding his lower abdomen. Temperature was 98.6° F., pulse 108, leucocytes 18,500. The abdomen was obese and there was marked tenderness in both lower quadrants, particularly the right, with rigidity. There was tenderness by rectum.

Only the resident staff saw this patient before operation and to them the diagnosis was not clear. It was agreed that the patient had peritonitis, probably due to appendicitis. Acute intestinal obstruction was ruled out. Some staff members unfamiliar with the gas stoppage sensation thought the original lesion a ruptured gastric ulcer or sigmoid diverticulum.

Operation revealed a ruptured appendix and generalized peritonitis. Histologically acute appendicitis.

Comments on Case 4.—Note the gradual onset suddenly becoming severe; also note how bowel consciousness dominated the clinical picture until the patient took a laxative and how the vomiting thus induced was what actually brought him to the hospital.

CASE 5.—A clinical clerk's history of a 27-year-old fellow student reads, "Chief Complaint: dull aching pain in right lower quadrant of fourteen hours' duration. Present illness: Last night about nine the patient had a feeling of epigastric distress and discomfort with a desire to pass flatus but inability to do so. This was followed in about one and one-half hours by a dull aching pain in the right lower quadrant, localized in the region of McBurney's point. This continued throughout the night. The following morning the patient had no appetite and passed two loose bowel movements. Today he has felt generally well except for constant dull aching pain. No nausea or vomiting. However, patient has not felt like eating today, although he took a cup of coffee and a slice of toast for breakfast, a coke and a cookie for lunch, and nothing since that time. At present complains of mild aching pain and tenderness in the right lower quadrant."

Examination showed a somewhat sick patient. The temperature was 97.6° F.; pulse 92; leucocytes 8,900, with stabs 2 per cent, segments 60 per cent, lymphocytes 34 per cent, monocytes 8 per cent. The abdomen was flat. There was local tenderness and rebound tenderness lateral to McBurney's point and tenderness by rectal examination. Diagnosis: acute appendicitis. Operation revealed an appendix swollen at its midportion. Appendectomy. Histological diagnosis: subacute appendicitis.

Comments on Case 5.—A straightforward case of acute appendicitis by every standard. It is interesting only because of the physicians

who examined the patient did not elicit the usual answers because, as happened in Case 3, he did not succeed in making clear to the patient that the questions referred to the onset. So much do the two pains differ that even a "mild" localized pain turns the patient's thoughts away from consideration of the onset discomfort.

CASE 6.—A 44-year-old hospital carpenter was referred by another physician in 1940. He complained of abdominal discomfort and was actually suffering from a sensation of gas stoppage. At that time no one could have had an inkling of this.

The history then taken was of lower abdominal cramps beginning two days previously and followed by no nausea or vomiting. He had taken milk of magnesia with slight result. Examination revealed no fever; leucocytes, 6,200; no localization of pain, and only a questionable tenderness at McBurney's point. Though he did not look very sick, he was sent to the hospital where he had a complete examination by the medical, surgical, urological, and otolaryngological services. He had a gastrointestinal series and a barium enema. No diagnosis had been arrived at when suddenly, twelve days after onset, the temperature and the leucocyte count rose; the patient clearly had a pelvis peritonitis, and the abdomen was explored. A perforated gangrenous appendix was removed.

Four years later the patient was questioned, in the light of our new beliefs. When asked what brought him to the hospital, he answered, "Not exactly a pain but a gnawing right in the center of my stomach." He said this "began on Monday, July 8, 1940. It started in the night. I felt O.K. the night before. It came on slowly. When I woke up in the morning, it seemed just a dull stomach-ache that I thought was cramps. I came to work thinking it would wear off. I didn't see a doctor till 1 P.M. Wednesday. In the meantime I got some milk of magnesia and took that with no relief. It bothered me all Monday night and still bothered me when I got up Tuesday and was a little worse. Tuesday I attended a funeral. The cramps seemed to be growing a little worse all the time so I went home from the funeral and stayed home the rest of the day. I felt pretty bad the next morning. I came in the hospital to see a doctor."

He then answered questions as follows:

"Do you remember trying at onset to move your bowels?"

"Yes, I tried to do that."

"With what results?"

"No results then."

"No gas?"

"No, there wasn't."

"Did the gnawing sensation at onset feel as if gas was stopped up inside you?"

"That's just the way it felt. I couldn't pass it one way or the other."

"Which seemed to be the way it wanted to pass?"

"It seemed to be more through the rectum."

Comment on Case 6.—The diagnosis was missed because pain did not localize. Four years after the event the story was elicited that would have saved him a dangerous illness. One wonders how he managed to remember those vague onset discomforts so accurately.

CASE 7.—I was the patient, taken sick on vacation. When I was admitted to the hospital, the admission note under date of April 20, 1941, was as follows: "Chief complaint: abdominal pain.

"Present illness: On Wednesday, four days ago, this 41-year-old white male physician was chilled while exercising. The next day he had general malaise and

a temperature of 101° F. He was out of town at the time but returned immediately and was seen at home by Dr. ——— who thought his condition was due to sinusitis. Except for headache, the patient had no subjective symptom of upper respiratory infection, but soon after returning to St. Louis his sinuses began to drain more than usual. His general malaise continued. He had three normal bowel movements and yesterday in the morning he began to experience abdominal pain. This was characterized as 'tugging' in character and generalized in situation. About 1 P.M. yesterday, after a light lunch, the pain became quite severe but let up toward evening, although it never disappeared completely. A few hours after a light supper the pain became very severe. Still of a 'tugging' nature 'as though someone were pulling on my mesentery.' He was kept awake all night and finally called Dr. ——— at 3 A.M. today. At this time there was generalized tenderness on examination with slight localization in the right lower quadrant. This morning the patient had no stool and passed no gas per rectum. Leucocytes 15,000. He took no catharsis but last night had a low enema with passage of a little gas and considerable relief. He had no nausea and no vomiting but took little fluid or food by mouth because it aggravated the pain. He was not febrile during the period of abdominal pain. He had no urinary frequency, burning, dysuria, pyuria, or hematuria.

"Temperature, 99.4° F.; pulse, 80; respirations, 20.

"Appears moderately acutely ill with sallow muddy complexion. Breath fetid, pharynx granular and injected. The abdomen is moderately obese, with little distention. There was no spasm or muscle guard. Minimal tenderness in right lower quadrant, medial and below McBurney's point. Gurgling sensation felt in the area of the cecum. Costovertebral area clear, genitals normal. There was no rectal tenderness or masses.

"Impression: sinusitis, probably subsiding appendicitis."

That evening, the symptoms having subsided, leucocytes having fallen to 8,200, and the temperature being normal, it was voted that I might return home. But I protested that, having lost a brother by acute appendicitis, I should prefer mine out.

April 23, appendectomy. The appendix was found gangrenous and ruptured. Histologically acute appendicitis.

Comments on Case 7.—One ruminates on one's near-tragedies. Yet it was two years before the histories taken from other patients with acute appendicitis began to evolve in my consciousness the notion that their early symptoms were the same as mine.

CASE 8.—A 24-year-old dental student entered the hospital complaining of suprapubic discomfort of twenty-four hours' duration.

The onset had been gradual, with a "full or stuffed feeling" vaguely referred to the lower abdomen. He volunteered the information that "it felt like gas stopped up inside." He immediately went to the toilet and passed a small, soft stool and a little gas. This partially relieved him. There was no anorexia. He vomited once.

Nine hours later a physician gave a laxative and a shot in the arm and told him he would feel well by morning. This satisfied the patient, who had had several previous brief similar attacks. Marked bowel consciousness and many unsuccessful efforts at defecation; only gas could be passed and the sensation was unrelieved. In the morning the symptoms subsided completely and the patient felt hungry and well.

The temperature was 99.2° F.; the pulse 72; the leucocytes 14,250, later rising to 18,400 with stabs 7 per cent, segments 75 per cent, lymphocytes 10 per cent, and monocytes 8 per cent; the urine normal.

The abdomen was absolutely soft though slightly distended, and rectal and abdominal examination by four different physicians failed to detect tenderness.

Chiefly because of the definite history of gas stoppage, appendectomy was advised. The appendix was found swollen, covered with fibrin, and bound down by adhesions. Histologically acute appendicitis.

Comments on Case 8.—Without the history, volunteered, of gas stoppage, this acutely inflamed appendix would not have been removed promptly, for there was no localization.

CHILDREN

What about children? We have seen so few of them that it does not seem fair to generalize. Some of the children with acute appendicitis proved by operation have eluded our attempts to elicit a story of gas stoppage, others have not. Further observation will be required to establish the reason for this. One case history is presented here. The story was obtained from the child, since the mother's story was misleading.

CASE 9.—A boy, 13 years old, was brought by his mother who said he had headache, fever and eye pains. **Present Illness:** She said that yesterday he complained of constipation for one day and took a laxative last evening, resulting in two bowel movements. The appetite was good, and there was no vomiting; he slept well last night. This morning on arising complained of headache, eye pain, and photophobia. He took aspirin this morning, attended school. No vomiting, good appetite. There were two bowel movements today. Yesterday evening slight epigastric pain. This has not recurred today. Temperature this afternoon was approximately 101° F. He was subjectively improved this evening. Questionable history of similar attacks before the age of five.

Let us compare this history of the mother's with one taken by a trained observer, Dr. M. M. Cook, directly from the same patient.

Chief Complaint: abdominal pain and fever.

Present Illness: Onset gradual and indefinite about noon yesterday, thirty hours ago, with vague abdominal discomfort which the patient described as an "ache." Not severe, but the patient "felt bad." He felt as if a bowel movement would relieve the distress and he made three unsuccessful trips to the toilet. Later, on his own initiative, he took a laxative (Ex-Lax), and several hours later had one small semisoft stool with some transient relief. He ate poorly at supper, slept all night. He awoke with some vague abdominal discomfort, not well localized but generally low in the umbilical. He had a headache and his "eyes burned." He took aspirin and went to school after a very meager breakfast of a slice of toast and water. He marched in the school parade and became very fatigued. He returned home, felt "very bad," took his own temperature (102° F.), and went to bed. There was dysphagia but not nausea. There is a history of several somewhat similar previous attacks, none this severe. No genitourinary symptoms. He had mild nasal congestion for several days, but no other upper respiratory symptoms.

Examination showed temperature 101.8° F.; pulse 80; leucocytes 7,000 with basophiles 2 per cent, eosinophiles 2 per cent, stabs 20 per cent, polymorphonuclears 60 per cent, lymphocytes 16 per cent. Face very flushed, with circumoral pallor. Jaws seemed full but there was no definite parotid or lymph node enlargement. Nasal mucosa was congested and the pharynx red. The abdomen was flat with a moderate tenderness in both upper and lower quadrants, and rebound tenderness. Marked tenderness on the right by rectal examination. **Diagnosis:** appendicitis. Appendec-

tomy was done the next morning, the appendix lying at the level of the umbilicus, with adhesions causing angulation, and a fecalith at the kink, with distal swelling. The peritoneal cavity contained increased clear fluid. Histologically subacute appendicitis.

Comments on Case 9.—Without the direct history from this 13-year-old boy the diagnosis would have been delayed, perhaps missed, because of the upper respiratory infection and poor localization. He answered the three questions Yes, Yes, No. The gas stoppage sensation established the diagnosis which otherwise was uncertain. The history as given by the mother was misleading.

DIAGNOSIS AFTER THE ATTACK

CASE 10.—A 20-year-old married woman was referred with the diagnosis of appendicitis because of two attacks within the preceding three weeks. Both attacks had lasted three days and had begun gradually with dull epigastric heaviness which she attributed to something she had eaten. She answered the three questions relative to gas stoppage sensation at onset, Yes, Yes, no. After onset she went to bed, and took a laxative. There was no nausea or vomiting. The bowels moved but without relief of the abdominal discomfort. There was anorexia, but no vomiting. After about twenty-four hours of discomfort of this type, pain localized in the right lower quadrant. There were no menstrual irregularities. She called a physician who diagnosed appendicitis and "froze it out." She spent three days in bed. A consultant recommended operation, for which she came to me. She was in the interval between attacks, with tenderness at McBurney's point the only positive finding. The leucocyte count was 8,800.

I found a more acutely inflamed appendix than expected, it being so friable that it ruptured during removal. Histologically subacute appendicitis.

Comments on Case 10.—The sensation facilitated the diagnosis of recurring acute appendicitis.

COMMENTS ON THE TEN PATIENTS IN GENERAL

The striking feature of the sensation of gas stoppage, as described by these patients, is the variety of names they spontaneously chose for it. Only one patient (Case 3) spoke of pain but since he also called it "a dull soreness," "a griping," and in answer to a question, "I can't describe it," the pain was certainly vague. Those who stuck to a single term said "gas stoppage," "cramps" or "griping" (three patients), "distress," "dull ache," "heaviness," "gas stopped inside," or "a stuffed feeling." I felt a "tugging," a "pulling on my mesentery." The patient reported as Case 6 felt "cramps," "a tight feeling," "not exactly a pain but a gnawing."

In contrast, in answer to question 1, every one of them accepted a "sensation of gas stoppage" as a precise description of what they felt.

Patients reported as Cases 2 and 4 noticed the feeling of gas stoppage during the onset but only some hours after the first discomfort began.

The discomfort at onset was always in the midline. Four patients spoke of the discomfort as generalized, four located it in the epigas-

trium, and one in the hypogastrium. The discomfort of the first patient moved from the hypogastrium to the epigastrium.

Note how real to the patient is the sensation of gas stoppage. Without cathartic or enema eight of the patients could not pass gas, six could not pass feces, and some of them struggled to do so (Case 4). Yet to the surgeon the gas stoppage remains a symptom, not a sign. It is an ineffective cramp. It disappears as localization occurs or when the appendix is removed.

Table I tells the rest of the tale. Note that five of the patients denied nausea and vomiting. Under prevailing methods of diagnosis the absence of these classical symptoms helps confuse the diagnosis. Equally confusing was the fact that localization was typical in only one-half the patients. (No statistical deduction is to be drawn from this; the cases were selected and are, in any case, too few.)

GAS STOPPAGE AT ONSET OF OTHER CONDITIONS

A. Present.—At onset most patients with acute intestinal obstruction show for a brief time clear-cut gas stoppage not distinguishable from that of acute appendicitis.¹ But this period is brief. Soon nausea and vomiting dominate the scene and localization occurs at the site of obstruction (for example, strangulated hernia).

One patient with terminal ileitis, without obstruction, and with inflammatory changes extending to the appendix, at onset had a sensation of gas stoppage. Similar early symptoms caused me to miss the diagnosis of a patient whose small intestine had been perforated by a toothpick.

B. Absent.—

CASE 11.—Perforated peptic ulcer. At 2:30 P.M. a young woman entered the hospital complaining of very severe abdominal pain.

Suddenly four hours previously she had felt a sharp pain on the left side over the fifth and sixth ribs. Previous attacks of similar pain had been diagnosed as pleurisy. The pain was severe, steady, not colicky. It “almost took her breath away”; she thought it was a heart attack. It radiated to the precordium and to the left shoulder but soon localized in the epigastrium. She found relief by lying on her right side. She tried to belch and took an alkali powder. She did not think of taking a laxative and did not go to the toilet. No nausea or vomiting.

She answered the two questions, Yes, Yes. But after consideration she answered the second question, No. In the end she said that belching rather than passing gas was what she felt would relieve her pain. Therefore, the sensation was absent.

The patient's actions, as usual, spoke louder than words. She took an alkali, not a cathartic. She made no attempt at passing gas or stool.

Actually the diagnosis was never in doubt. Physical signs pointed to a perforated peptic ulcer; x-ray with the patient in the upright position showed free air under the diaphragm.

CASE 12.—Acute cholecystitis. A 75-year-old man, complaining of severe abdominal pain, was sent to the hospital; diagnosed, acute appendicitis.

Onset sudden at 9 P.M. the night before, after retiring. The pain felt "like a boil underneath there," the patient pointing just beneath the right nipple, with a "pulling this way," pointing to the epigastrium.

The pain, then, was definite. By morning it had worked down to a point one inch above the right anterosuperior spine somewhat posteriorly. It felt "like a bag of potatoes." For relief he went once to the toilet but he effort to pass gas or to have a movement was in vain. Then he vainly tried to vomit. He took a laxative and made no further efforts at stool until a normal movement the next morning. This did not relieve the pain.

No nausea or vomiting. No previous attacks.

He answered the question, Yes, No, No. He felt that relief might have been had by passing gas upward. Therefore, the sensation was absent.

A ruptured gall bladder was found at operation.

CASE 13.—Ruptured ectopic gestation. The patient, a 37-year-old woman, had been married ten years and was childless. No menstrual irregularities before admission.

Ten days previously, while working in a store, she felt nauseated. Shortly thereafter there was sudden, definite pain in the right lower quadrant which lasted one hour, then disappeared completely. (The last menstrual period had been a week before this and normal, but there had been a little spotting just before onset.) After the pain disappeared, the patient felt as usual for ten days and kept on working. Then the spotting, nausea, and sudden pain recurred. This time the pain became steadily worse and rapidly incapacitating, and nine hours later the patient was brought to the hospital in an ambulance.

Questions 1 and 2 were answered, Yes, Yes, but this feeling lasted no more than an hour. The pain was not in the midline, as it should have been at the time of a real appendical gas stoppage. The pain was sharp and had been preceded by nausea and spotting on two occasions.

She was referred to a gynecologist who found at operation a ruptured ectopic pregnancy on the right side and dermoid cysts of both ovaries.

CONCLUDING REMARKS

The surgeon who finds time to sit by the bedside and listen to a patient's vague, rambling story of the onset of an attack of acute appendicitis (and then aim at the heart of it with his three questions) will discover that the words quoted in this paper by no means cover the names a man can call a cramp in his middle. And if the surgeon is interested to study how movements (inward or outward); position, digestion, atmosphere (smoky), etc. aggravate or do not aggravate the discomfort at onset, he has a job cut out for him—and after such study doubtless the surgeon will have a name for it himself.

The writer of a clinical paper is inevitably indebted to the bedside battles that have clarified his notions for him. Many discussions in the Student Health Clinic satisfied Dr. M. M. Cook and me that the phrase "bowel consciousness," suggested by him, best expresses the patients' sensations, but the patients themselves proved to us that "sensation of gas stoppage" says something to them.

How different the second pain, the pain of localization! This is as precise as the onset discomfort is vague: precise in time of onset,

precise in situation, precise in quality; "it feels like a boil," "like a toothache," "a real pain," "right there."

What we have called the sensation of gas stoppage occurs during the onset (and only during the onset) of acute appendicitis, prior to "localization." Studies in progress since a former paper was published in February, 1944,¹ suggest that the sensation of gas stoppage is present during the onset of forty out of fifty proved cases. Sufficient experience has not accumulated to warrant a more specific statement.

But this may be said: The patients from whom we have failed to get a convincing story are (a) children, (b) patients with a low I.Q., and (c) patients who begin their attack in mid-career, as it were, with the pain of localization and without the brief, vague onset period that has been so repeatedly described in these pages. It seems, up to the moment, that the more fulminating cases (for example, Case 4) tend to exhibit the clearest picture of gas stoppage. Should further experience confirm this hint, study of the onset symptoms will indeed be worth the surgeon's while.

And what conditions other than acute appendicitis show at onset the symptoms of gas stoppage? Notably small intestinal obstruction and other less usual diseases of the small intestine.

What, then, of errors resulting from this attempt to establish a diagnosis of acute appendicitis before localization? There have been errors enough but all they have taught us is to study the early history of the attack more precisely and ever more precisely. The cases cited hint at some of the difficulties encountered.

The battle of the bedside! One questions, sometimes, whether the triumphs of the operating room impart so fierce a joy! Let us not forget, when pressed, that at the battle of the bedside the patient is on our side, if we happen to be right.

The suggestions herein contained will not make the battle of the bedside any less sharp. Nor will the acceptance of the patient's onset history as part criterion for the diagnosis of acute appendicitis, in a sense, make this diagnosis any easier. It is a long, tedious job to take a good history.

SUMMARY

1. A vague midline sensation of gas stoppage characterizes the onset of acute appendicitis.

2. It induces the patient (a) to seek the toilet (b) to take laxatives.

3. During the time of onset, a period from one to more than twenty-four hours, few patients are able to pass gas or to defecate without catharsis or enemas. Those able to pass gas or to defecate obtain little or no relief thereby. Hence, the sensation is a symptom and not a physical sign.

4. This bowel consciousness is an urge downward rather than an upward urge of nausea or vomiting.

5. The sensation of gas stoppage ends when pain localizes over the appendix, usually in the right iliac fossa. The features described are then altered. There is a definite pain which is different.

6. The gas stoppage sensation is present at onset irrespective of whether localization later is "typical," "atypical," or absent.

7. The sensation is particularly valuable in fulminating cases.

8. Three questions have been devised to elicit it. To find it, the examiner should carefully focus the patient's mind on the time prior to localization of pain, to the time not when he first felt sick, but when he last felt perfectly well.

REFERENCES

1. Keyes, E. L.: Diagnostic Features of the First Pain of Acute Appendicitis, *J. Missouri M. A.* 41: 30-33, 1944.
2. Richardson, E. P.: Diseases of the Appendix, Small Intestine, and Colon in Graham, E. A.: *Surgical Diagnosis*, Vol. II, Ed. 5, Philadelphia, London, 1930, W. B. Saunders Company.
3. Homans, J.: *Textbook of Surgery*, Springfield, Ill., Baltimore, 1940, Charles C. Thomas, Publisher.
4. Fitz, R.: Quoted by Homans.³
5. Murphy, J. B.: *Surgery of the Appendix Vermiformis*, in Keen, *Surgery*, Philadelphia and London, 1908, W. B. Saunders Company.

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rectum are due to both factors, namely, injury of the extrinsic nerve supply of the urinary bladder, and interference with the normal supportive structures of the bladder neck and posterior urethra.

Urinary retention usually follows immediately on completion of the surgical procedure and, unlike retention which so frequently complicates most operations, it may persist for days, weeks, or on some occasions even months. Failure of the bladder to expel urine responds to one type of treatment or another, only to recur at some later date.

Paradoxical incontinence is not an unusual manifestation in some of these cases, especially in the later phases of convalescence, and frequently requires the use of mechanical devices designed to prevent soiling of clothing.

The presence of varying amounts of residuum may persist for long periods following operation, even though patients may urinate with no apparent difficulty. In women procidentia frequently aggravates the condition, while in men the presence of enlarged prostates may intensify the difficulty.

Prevention.—Probably the most important problem associated with the prevention of urinary retention in this group of surgical cases is recognition and correction of conditions which are actively causing, or which can give rise to, obstructive uropathies. It seems to me in the light of my experience that a woman with a well-defined cystocele, particularly when associated with urinary retention, should have a perineorrhaphy performed before undergoing the radical operation for rectal carcinoma. This view is, admittedly, not that of many eminent surgeons. In male patients, every effort should be made to elicit pertinent and precise information regarding urinary difficulties. In the event the patient presents suggestive symptoms, a thorough cystourethroscopic study of the vesical neck and posterior urethra is indicated. Should the examination disclose an obstructing prostate, a median bar, or vesical neck contracture, experience has dictated to me that appropriate measures must be carried out to correct them before intestinal surgery is undertaken. Again, it seems to me that transurethral resection, wherever possible, is the procedure of choice, and can be expeditiously performed a few weeks prior to the intestinal resection. This is a purely personal view of the matter, which is hardly shared by surgeons in general.

The presence of urinary residue which cannot be accounted for by an obstructing lesion warrants a complete neurologic investigation and cystometric study. Attempts at correcting or improving atony of the vesical detrusor by cholinergic drugs such as doryl, furmethide, or others should be made prior to operation. Failure to obtain improvement warrants the performance of suprapubic cystostomy immediately following the radical operation for carcinoma of the rectum.

I believe a procedure well worth trying as an aid in preventing impairment of vesical function subsequent to surgery is the introduc-

tion of an indwelling urethral catheter for continuous tidal drainage immediately before the operation, to be left in situ during the course of the operation and for a week or ten days after.

Gentle and careful handling of tissues during the perineal phase of the operation, especially during the stage of separation of the rectum from the bladder, will greatly minimize the risk of this complication. Another important factor in preventing postsurgical vesical atony is proper packing of the perineal wound following extirpation of the rectum, in order to give ample support to the bladder neck during the early stages of convalescence.

Treatment.—The active treatment of acute or subacute urinary retention occurring during the convalescence from radical surgical removal of carcinoma of the rectum consists in tidal drainage for at least ten days following the onset of symptoms. Should the procedure fail to restore full vesical function, cholinergic drugs may be tried along with measures designed to cause the expulsion of urine from the atonic bladder through manual abdominal wall massage carried out at regular stated intervals, as is employed in treating those afflicted with other varieties of neurogenic bladder disturbances.

It has been my experience that most patients with urinary retention eventually respond to conservative treatment. Before discharging a patient as cured, it is necessary to ascertain whether or not the bladder empties completely after voiding. Since the tendency toward recurrence of urinary retention in this group of patients is not infrequent, it is advisable to have them return at least every four months in order to determine the amount of residuum present. Excellent results often follow the method of gently overdistending the bladder with a 2 per cent solution of boric acid once or twice weekly.

In the event obstructive uropathies have been overlooked or had not been removed prior to operation, prompt corrective measures should be undertaken following the onset of symptoms which suggest vesical dysfunction. It is obvious that careful cystourethroscopic studies are of the utmost importance before the institution of corrective therapy.

UROSEPSIS

Urosepsis is a complication which must be assiduously watched for in all patients subjected to radical operations for carcinoma of the rectum. This complication is more or less dependent upon a variety of conditions, some of which antedate the surgical procedure, and others which follow. It is of the utmost importance for any surgeon contemplating a radical operation for carcinoma of the rectum to ascertain the exact status of the urogenital tract. Among the more common conditions predisposing to postsurgical urosepsis are (1) the presence of obstructive uropathies such as vesical neck obstruction from hypertrophic prostates or median bars in men, and cystoceles in women; (2) active infections within the prostate, bladder, or upper

urinary tract; and (3) spreading infection from an ulcerating carcinoma of the rectum to the bladder by way of the regional lymphatics or by direct extension.

The most important factor in the etiology of urosepsis following radical surgery for carcinoma of the rectum is the loss or impairment of expulsive power of the detrusor muscle, leading to urinary stasis. Another causative factor, although of less importance, is the hazard involved in frequent catheterization of patients with atonic bladders. Patients with carcinoma of the rectum have a lowered resistance to all varieties of infection, and are in many respects comparable to patients with neurogenic bladders following transverse myelitis of the cord, where resort to frequent catheterization is definitely contraindicated.

Following extirpation of the rectum, a large cavity results which lies adjacent to the posterior vesical wall. This cavity, in a large percentage of patients, becomes infected immediately following the surgical procedure, or shortly after. I believe that this eventually leads to pericystitis, and is therefore another important cause of post-surgical urosepsis.

Prevention.—The prevention of urosepsis in these patients depends upon its detection prior to operation, and upon the recognition of conditions within the urogenital tract which have a predisposing tendency to infection. It is obvious that in order to discover infection or predisposing factors that may lead to infection, it is necessary to subject the patient to a thorough investigation of the genitourinary system prior to operation. This requires a complete cystourethroscopic examination, pyelography, and bacteriologic study of the segregated urines. Correction of factors predisposing to infection, such as obstructive lesions anywhere along the genitourinary tract, should be accomplished before the colonic operation is performed. Chemotherapy is instituted to control existing infection. Frequent interval examinations of the urine should be made and the emptying capacity of the bladder determined for at least one year following operation, in order to avoid urosepsis which may occur late in the course of post-surgical convalescence.

Treatment.—Urosepsis which develops after operation should be treated along orthodox urologic lines. Chemotherapeutic agents administered orally or parenterally as conditions warrant, accompanied by free urinary drainage, are the prime features in the therapeutic program. In the event that the source of the trouble is in the lower urinary tract, the procedure of choice is tidal drainage through an indwelling urethral catheter, or better still, through a suprapubic cystostomy tube. However, it appears to me, but may be arguable by other surgeons, that if the condition is in the upper urinary tract, ureteral catheter drainage or drainage through a nephrostomy tube may become necessary.

INJURY OF THE URINARY TRACT

Injuries to the genitourinary tract most likely to occur during the course of a radical resection of the rectum are (a) injury of one or both ureters, (b) injury of the bladder, and (c) injury of the urethra. Injury of the ureters may occur during the abdominal stage of an abdominoperineal resection, and less frequently during the perineal stage. The bladder and urethra are liable to be injured during the perineal stage of the operation.

Prevention.—Because of its closer proximity to the pelvic portion of the rectum, the left ureter is more likely to be injured than the right during the abdominal stage of the operation. To minimize this danger, the following steps should be followed: (1) following the re-establishment of the pelvic diaphragm, inspect the ureters to assure their continuity and patency. (2) Should either be inadvertently injured, immediate repair is recommended.

To avoid injury to the lowermost ends of the ureters may be injured during the abdominal stage of the operation, the more likely injury of the bladder or posterior urethra must be guarded against. The introduction of a urethral catheter will obviate, or at least greatly minimize, the danger of injuring the bladder, good visibility of the surgical field during the abdominal and perineal stages is of the utmost importance. This is particularly true when liberating the rectal part from its anterior and lateral attachments. Another important factor is securing perfect hemostasis in order to avoid blind clamping and the use of mass ligatures in a field obscured by blood. Clean sharp dissection and the establishment of clear planes of cleavage in separating the rectum from the bladder will greatly minimize this risk. It is also important to recognize the presence of vesical wall infiltration by the tumor, which tends to expose the bladder to accidental injury during the course of dissection. And finally, in the event that the bladder is accidentally opened, it is necessary to close the opening promptly in layers and to introduce an indwelling urethral catheter which should be permitted to remain in situ for a week or ten days after operation.

Treatment.—Postsurgical injuries of the ureter should be treated in the same manner as injuries resulting from any other cause. End-to-end anastomosis of the divided ureter, using a splinting ureteral catheter or T tube, preferably with a complementary nephrostomy, or implantation of the proximal end of the severed ureter into the bladder when feasible, or nephrectomy providing the other kidney had been previously found functionally adequate to maintain life are the procedures generally recommended. It is perhaps needless to state that

the prompt repair of an injured ureter will yield better results and will entail less difficulty in repairing than when left for some later date.

Injuries of the bladder or urethra, like injuries of the ureter, should be repaired immediately. In the bladder, for example, the opening is promptly closed with two layers of fine chromic catgut, avoiding the inclusion of vesical mucosa in the line of sutures. This is to be promptly followed by the introduction of an indwelling urethra catheter which is permitted to remain in place for a week or ten days. The use of sulfonamide drugs is of value here.

The surgical problem becomes much more complex when with repair of vesical fistulas, particularly of the perineal type, which usually occur late in the postsurgical course. This is due to the thickness of the tissue which makes it difficult to expose the edges for suture. A step essential to successful closure. I have found the use of a Young boomerang needle of inestimable value in the repair of vesical fistulas. In the latter type of case I have found the following procedure consisting of a suprapubic cystostomy and

perineal closure at a reasonable interval, by perineal closure upon its completion. In the interim between the first and second operations, proper cleansing of a perineal wound, which is usually grossly infected when the patient first comes under observation, and also upon bolstering the patient's resistance and physical stamina.

During the final stage of the operation the patient is placed in the prone position, or prone with thighs depressed. The original wound is enlarged and deepened down to the bladder. All granulation tissue leading down to the fistulous opening in the bladder is removed and the edges of the bladder constituting the mouth of the fistula are freed and inverted with interrupted fine chromic sutures introduced through a Young boomerang needle. To test the accuracy of closure, a small amount of indigo carmine or methylene blue solution is introduced into the bladder through a suprapubic tube in order to see whether any escapes into the perineal wound. The overlying wound is then salted with sulfanilamide crystals and closed in layers. Before removing the suprapubic tube, it must be definitely ascertained that (a) the perineal wound is solidly healed, and (b) the urethra is fully patent. To be assured of the patency of the urethra throughout its entire length, it is necessary to be able to pass freely bougies of reasonable caliber into the bladder.

In repairing defects of the posterior urethra, which is the segment of urethra most likely to be injured during the perineal stage of the operation in male patients, the same fundamental principles hold good as in the repair of injuries of the urethra following other causes. Small openings frequently heal following the use of an indwelling

urethral catheter. When larger parts of the urethra are involved, various plastic procedures can be carried out through fresh incisions in the perineum similar to those employed in perineal prostatectomy. Similar procedures can be performed by reopening the original sacral wound. A preliminary suprapubic cystostomy greatly facilitates healing in this group of patients.

SUMMARY AND CONCLUSIONS

This article deals with the prevention and treatment of the more common urologic complications which may follow the radical operation for carcinoma of the rectum. An attempt has been made to explain the underlying causes of these complications in order to facilitate a more comprehensive understanding of the principles employed in the prevention and management of each complication.

THE CONSERVATIVE AND OPERATIVE TREATMENT OF LESIONS OF THE INTERVERTEBRAL DISCS IN THE LOW BACK

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DURING recent years the conviction is growing that the symptom which we formerly attributed to sacroiliac or lumbosacral strain, arthritis or subluxation, lumbosacral facet syndrome, postural strains of the low back, and myofascitis or fascitis in the lumbar region are really due to lesions of the intervertebral discs in this area. This is especially true in patients with sciatic pain. These do not include all patients with sciatica but are the large group of patients with obscure low back pain without sciatica in which the general physical and laboratory examinations and the x-rays revealed no explanation of the symptoms, except possibly a narrowing of one or more intervertebral discs.

Investigators have sought to explain the symptoms in these low back conditions with the hope that once the pathology was satisfactorily demonstrated it would be possible to formulate a logical therapeutic attack on the lesion and thus treat these patients with confidence, precision, and uniform success.

No, that the pathology is known it seems right and logical to remove the protruding nucleus pulposus and relieve the patient promptly and completely. Unfortunately, this involves a rather difficult major operation and after this has been done a few patients complain of the same pain, disability and a considerable percentage of them are not completely relieved. In focusing our attention on the protruding disc we are apt to ignore the fact that these lesions occurred just as frequently in the past as we do today and that in the past it was possible for us to relieve the great majority of our patients without operation.

The methods which we used were rest, traction, heat, support to the low back, correction of body mechanics, deep x-ray therapy, manipulations with or without anesthesia, and finally fasciotomy, operative fusion of the sacroiliac joints or the lumbosacral spine, or fusion with resection of the articular facets. We treated the patient conservatively over a considerable period and resorted to surgery only in those instances where prolonged conservative treatment had failed to relieve the pain and disability and where these symptoms were sufficiently severe to warrant a major surgical procedure followed by a prolonged convalescence.

Now that we know where the pathology lies there is no reason why we should not continue the same general plan with the amendment that we now have something more definite in the field of surgery to offer these patients if prolonged conservative treatment has failed to relieve their symptoms or if circumstances make conservative treatment impractical.

It is to be noted that the severity of the symptoms and the degree of disability vary greatly in different patients and at different times in a given patient. The same is true of the findings on physical and neurologic examination. One patient may complain of a mild pain in the low back which occurs occasionally after prolonged standing or sitting or strenuous exercise and another may be confined to bed with a severe pain in the low back which radiates down the back of the thigh and leg to the foot and is lessened but not relieved by certain postures, but becomes agonizing with the slightest movement.

In the first patient the physical examination may reveal nothing abnormal and in the second patient pain may prevent a satisfactory examination. It is also to be noted that the mild symptoms may become severe after a strain of the low back or without known cause and the severe symptoms may subside with or without treatment. It is thus understandable why many patients give a history of previous attacks. A condition which is characterized by recurrences must also be characterized by remissions.

Our assumption that the mild low back pain and the severe pain with sciatica, and all gradations between the two extremes, are due to lesions of the intervertebral discs in the lower lumbar region is based on the operative finding of disc lesions in the more severe cases and the repeated clinical observation that not only are all gradations between the mild and the severe cases seen in different patients, but the progression or regression of signs and symptoms may be observed in a single patient.

Study of a series of patients suggests that the low back pain may be due to the lesion in the annulus fibrosus or a midline protrusion and the sciatic pain to irritation of a nerve root by a lateral protrusion of the disc.

In planning the treatment of these patients it is necessary to adapt the treatment to the patient and his symptoms. In the great majority of instances the patient is able to continue his or her normal occupation and is treated as an office patient. In others change of occupation is necessary. In the presence of severe pain and disability, rest in bed is advisable until the pain subsides or is relieved. Operation is reserved for those who do not respond to conservative treatment and who are sufficiently disabled to render operation justifiable and to those in whom prolonged conservative treatment is not practical. We can thus divide the patients into three groups: the ambulant, bed, and operative groups.

The diagnosis is made and the type of treatment indicated for a given patient is determined from the history and physical examination. In many cases the history is more important than the physical examination. This is because the findings on physical examination depend largely upon the severity of the symptoms present at that time and these may vary from day to day, and even from hour to hour. Frequently, a patient with a suggestive history is asked to return for a second examination when pain is present after exercise, prolonged standing, or whatever aggravates the pain in this particular patient. This is especially true with a history of prolonged disability which has not been relieved by conservative treatment and where operative treatment is being considered.

Routine x-rays of the lumbosacral region are made to rule out disease or spondylolisthesis or to note congenital anomalies, if present. In cases of long duration the x-ray may supply confirmatory evidence of an intervertebral disc lesion, as the space between the bodies of two vertebrae may be narrowed. But it is to be noted that even in these instances the symptoms may arise from a neighboring disc which presents a normal appearance in the x-ray.

No laboratory examinations or elaborate medical surveys are necessary before beginning treatment of the average patient. These patients are normal individuals who have a low back strain. Before operation they should have a general physical examination, just as should any other patient who is to be subjected to a major surgical operation.

Spinograms are not done. If the patient is to be treated conservatively the exact location of the lesion is of no importance. If he is to be operated upon the location of the point of tenderness in the back directly over the lesion, the distribution of the pain, and the neurologic findings enable an experienced clinician to localize the lesion as accurately as can be done in a spinogram. In addition, many surgeons routinely explore two discs at operation.

Treatment of Ambulant Patients.—Ambulant patients are treated by support to the low back, manipulation, stretching of the low back, and correction of body mechanics by exercise, a hard flat bed, vitamin B, weight correction and salicylates, and change of occupation if necessary.

A support which tends to flatten and immobilize the low back is prescribed for practically all of these patients. The women are given a corset or girdle which grasps the pelvis and extends up to about the tenth dorsal vertebra. This has stays up the back and can be laced or strapped tightly around the body. Men are given a wide canvas belt of about the same dimensions which has stays but no pad in the back and straps or lacing in front. The belt is narrowed in front to permit sitting (Fig. 1). Many patients when first examined are wearing a narrow canvas sacroiliac belt with a pad. These are less efficient than

the wide belt and are discarded. When more rigid support is needed a signet ring plaster of Paris jacket or belt is applied. This is wide behind, extending from about the tenth dorsal vertebra to the lower sacrum and is narrow in front, being shaped like a signet ring. It is applied with the lumbar spine flat or flexed. The patient grasps an iron upright, places his feet against its base and sags backward, retracting his abdomen while the plaster is being applied. After it has hardened the plaster is trimmed in front to permit sitting and bending.

If immediate support is indicated for acute symptoms the back is strapped with adhesive. The patient lies prone with a pillow under his abdomen, and the cross strapping begins at the midaxillary line at the level of the trochanter and extends up to grasp the lower two or three ribs. This is worn for about ten days, or until a removable support is obtained.



Fig. 1—Lumbosacral belt as used for low back pain. (Three views)

Manipulation—The object of the manipulation is to widen the space between the posterior parts of the bodies of the vertebra and thus cause retraction of the disc. Only three maneuvers are used routinely. The patient lies on the unaffected side facing the surgeon with the upper (affected) leg hanging over the side of the table. The surgeon grasps the patient's shoulder with one hand and places his opposite forearm on the crest of the ilium. When the patient is relaxed the surgeon delivers a quick thrust and pushes the ilium down and forward while the shoulder is pushed up and back. This movement may produce a crunching sound and frighten the patient, but rarely causes pain. The manipulation is repeated on the opposite side and the patient is then turned on his back and both knees are strongly flexed on the abdomen, thus flexing the lumbar spine. These manipulations may be followed

by a variable amount of relief or they may be ineffective. The back may be strapped with adhesive after the manipulation.

Body Mechanics.—The patient is taught to sit, stand, and walk with the head up, chin in, chest up, abdomen in, back flat, and hips in. He is also given exercises to strengthen the abdominal, back, gluteal, and lower extremity muscles and to flex and stretch the lumbar spine and elevate the diaphragm.

Bed.—A piece of plywood cut to fit over the springs or boards placed lengthwise are put between the mattress and the springs and a firm mattress is advised. This is not insisted upon if, after a fair trial, the patient is more comfortable in an ordinary bed.

The patient's diet is regulated in an effort to cause his weight to approach the normal for his age and type. He is given about six times the daily requirement of vitamin B complex. This has a tonic effect, gives most patients a sense of well-being and makes them feel better. If the pain is sufficiently troublesome the patient is given aspirin or some other form of salicylate and, rarely, small dose of codeine, or he may use local heat to the low back at night for pain. He is advised to avoid heavy lifting, stooping, prolonged standing, or whatever seems to him to aggravate the pain.

As the symptoms subside this regime is gradually discontinued.

Treatment of Bed Patients.—Bed patients are those in whom the symptoms are so severe that they are not able to carry on their daily routine; rest in bed is advisable and is an important part of the treatment. They should be hospitalized, but most of them either cannot get a bed in a hospital immediately or do not want to go to a hospital, so they must be treated at home. They are advised to place boards between the spring and the mattress and to remain in bed most of the time, lying on the back with large pillows under the head and knees or on the unaffected side with the hips and knees flexed (in order to maintain flexion of the lumbar spine). Local heat, either dry or as hot fomentations, is applied to the low back and the patient is instructed to get in a tub of hot water once or twice a day and when relaxed to flex the knees strongly on the chest, thus stretching the lumbar spine in flexion. The local heat and hot bath are omitted if the back has been strapped with adhesive.

Codeine and aspirin are given every four hours for pain and the manipulations described may be used; if necessary, morphine may be given before the manipulation in order to secure relaxation.

If the patient is hospitalized he is kept in bed and is denied bathroom privileges. The manipulation may be performed under avertin or general anesthesia and when this is done forcible straight leg raising, hyperextension of the hips, and strong traction obtained by suddenly jerking the leg downward are added to the maneuvers described.

As the acute symptoms subside the patient is given exercises to strengthen the abdominal muscles, flex the lumbar spine, and correct his body mechanics. He is gotten up gradually with support to the low back and is permitted to resume his normal activities as the symptoms subside. The ambulatory treatment is then continued until the patient is free of symptoms or until operative treatment is advised and accepted. No effort is made to keep the patient in bed until the symptoms are completely relieved, because experience has shown that prolonged rest in bed rarely cures a lesion of the intervertebral disc.

In some clinics injections of novocain into the painful areas are used and reports in the literature indicate that this form of treatment gives permanent relief in a high percentage of the patients. I have tried the method, but with indifferent success, perhaps because I used it only in patients who did not respond to the methods mentioned previously. The same is true of prolonged traction in bed.

If persisted in over a reasonable period the procedures mentioned will result in relief in a high percentage of the patients (probably about 90 per cent) and most of these will be able to return to their former occupations and be free from symptoms. It is to be noted, however, that some patients may have recurrence of the symptoms, either spontaneously or following strain of the low back. The only conservative methods preventing these recurrences are the avoidance of strain and the maintenance of good posture, and these are not always effective.

Treatment by Operation.—If conservative treatment is unsatisfactory, the patient is not relieved or is intolerant of his symptoms and demands relief by surgery, or if he has a long history of disability which has not responded to treatment elsewhere, operative treatment should be considered.

The operation consists of removal of the protruding disc with or without curettement of the nucleus pulposus and with or without fusion of the spine in the involved area. The operative technique varies widely among different surgeons and if the best results are to be obtained it should be performed by a surgeon who has had considerable experience in this field or who has visited other clinics and observed the technique of surgeons who have had this experience.

The operation may be relatively simple, as the extruded disc may present itself immediately beneath the ligamentum flavum and the nerve root can be retracted and the protruding disc lifted out. On the other hand, the surgeon may encounter profuse bleeding from the extradural veins and have considerable difficulty in controlling this to a point where he can make a satisfactory examination of the disc; then he may have difficulty in deciding whether he is dealing with a normal disc or a hidden disc, as described by Dandy.¹

Operative Technique.—The technique is as follows: The patient is placed in the prone position with a pillow under the lower abdomen and

the hips moderately flexed to flatten the lumbar spine. A pad is placed under the unaffected side of the pelvis to tilt the back of the patient toward the surgeon who stands on the affected side.

The operation can be performed under general or local anesthesia (1 per cent novocain for the skin and the nerve roots and $\frac{1}{2}$ per cent for the other tissues). The novocain contains 4 drops of adrenalin to the ounce. Preoperative medication consists of 3 gr. of nembutal and $\frac{1}{6}$ or $\frac{1}{4}$ gr. of morphine when local anesthesia is used.

The skin and subcutaneous tissues are infiltrated with novocain and a straight incision extending from about the third lumbar to the second sacral spine is carried down to the spinous processes. The bleeding is controlled. The tissues on either side of the spinous processes are infiltrated and then the needle is directed outward to the vicinity of the articular facets and lamina and the deep tissues are infiltrated on the affected side. Skin towels are applied and with a knife and a sharp chisel and periosteal elevator the spinous processes of the fourth and fifth lumbar vertebrae are exposed subperiosteally. On the affected side the tissues are stripped from the lamina and the perium well out to expose the articular facets and a self-retaining retractor is inserted. With a large curette and a sponge the ligamentum flavum between the fourth and fifth lumbar and the fifth lumbar and the first sacral vertebrae are cleaned of the fat tissue which lies over them. At this point the spinous processes are grasped with a heavy toothed artery clamp and manipulated up and down in the horizontal plane or are pushed upon with an osteotome in order to demonstrate any abnormal mobility. Dandy considers abnormal mobility of the spinous process a pathognomonic sign of an abnormal intervertebral disc. I consider it confirmatory evidence, but rely more on the history and physical examination of the patient and visual examination and palpation of the disc. Likewise, I have not always been successful in identifying the ruptured disc by pressure on the ligamentum flavum. If the nerve root is pushed back against the ligament the pressure will cause sciatic pain, but in many instances the nerve root is some distance anterior to the ligament and in these pressure on the ligament does not cause pain.

If a lesion of the lumbosacral disc is suspected the ligamentum flavum is separated from the deep surface of the inferior margin of the lamina of the fifth lumbar vertebra with a thin curved periosteal elevator or chisel. A good-sized button of bone comprising about one-half of the width of the lamina and extending as far laterally as possible is removed with a rongeur.

It is possible to remove many discs without removing any bone and I have done so, but have discontinued the practice because a much more satisfactory operation can be performed and the bleeding controlled more effectively if an adequate exposure is obtained in the beginning. And the removal of the button of bone from the lamina does no harm. A

similar button of bone may be removed from the superior margin of the sacrum if necessary.

The ligamentum flavum is then nicked with a small knife, care being taken not to incise the dura. It is grasped with an artery clamp and excised as completely as possible in one piece. Any remaining tags of the ligamentum flavum which may obstruct a clear view of the disc are also excised. The extradural fat is retracted or picked out to expose the nerve root and this is injected with about $\frac{1}{2}$ c.c. of 1 per cent novocain. The nerve root is very sensitive and even when the injection is done with a very fine needle on a tuberculin syringe this may cause a severe pain down the patient's leg. This is almost the only pain suffered by the patient after the initial infiltration of the skin. The nerve root is usually injected through the ligamentum flavum as soon as this structure is cleaned off, but this is not always successful.

It is during or after the removal of the ligamentum flavum that the intraspinal bleeding is encountered and a sucker is necessary to remove the blood from the field. The bleeding is controlled by cottonoid sponges wet with normal saline solution which are packed against the bleeding points and sucked dry with the sucker. These sponges are of two types: (1) strips about one-half inch wide and six inches long and (2) small squares about three-fourths inch across which have a black thread about twelve inches long sewn and tied in the center to prevent loss in the wound. Care is taken not to rupture the thin-walled extradural veins, the largest of which lie near the lateral wall of the spinal canal, but frequently this happens and the surgeon may be working in a pool of blood with a questionable protruding disc in the bottom of the pool, unless he has learned to control this bleeding by suction and packing. I have not used the electric cauterly inside the canal for fear of injuring the nerve root.

The surgeon holds the sucker in his left hand and manipulates the cottonoid sponges or a small spatula or blunt dissector with his right. An assistant may retract the nerve root toward the midline with a narrow retractor or the surgeon may hold it over with the tip of the sucker to expose the protruding disc beneath it. In many instances the nerve root is firmly adherent to the protruding disc and must be dissected free before the nucleus can be removed. Usually this can be done by blunt dissection with a small spatula or blunt dissector. The dura may be torn during this procedure and some spinal fluid may escape. I have not tried to suture these small tears in the dura and have not noted any bad effects afterward. If troublesome, they may be closed with a bit of crushed muscle.

In other instances the nerve root is not adherent and is easily pushed aside to expose a glistening disc which is bulging slightly or markedly, but which is not ruptured. When this is pressed upon by a blunt instrument it is found to be compressible or like rubber. This is the concealed

disc described by Dandy. The normal disc is flat and quite firm on pressure, especially when the lumbar spine is flexed.

If the disc is ruptured and extruded the nerve root is retracted toward the midline and the extruded material is removed with a clamp or forceps to expose the cavity beneath. This cavity is then curetted lightly with a medium-sized curette in an effort to remove as much as possible of the nucleus pulposus and thus prevent a recurrence of the protrusion. In using a curette or forceps in the cavity of the disc, care is taken to introduce the instrument gently and not push it in forcibly, as it is possible to penetrate the anterior ligament and injure the aorta. Moderate force may be used in curetting the surface of the vertebral bodies and in pulling the curette out. However, no effort is made to break through the plate of cartilage and bone and expose the underlying cancellous bone with the expectation that the bodies of the vertebrae will then fuse. As a matter of fact, perforation of this plate is avoided.

If the disc is not ruptured a rather large window is cut in its protruding surface, using a tenotome or a urethral knife and, after the loose material is pulled out with forceps, the disc is curetted lightly and an effort is made to remove as much of the nuclear material as possible.

Unless the surgeon is fairly well satisfied that only one disc is causing symptoms, the adjacent disc is exposed and examined and treated in the same manner if it is found to be abnormal. If the first disc exposed is found to be normal the adjacent disc is exposed and examined as a routine procedure and is removed if it is found to be abnormal. If the two lower discs are normal the one between the third and fourth lumbar vertebrae is exposed and examined and removed if it is abnormal. This is apt to be the site of the lesion if the patient has had pain in the groin or anteromesial aspect of the thigh.

Occasionally, in older patients with symptoms of long duration the disc has become obliterated and a ridge of bone is present along the margin of the vertebral body beneath the nerve root. When this is found the nerve root is retracted medially and the ridge of bone is removed with a small thin osteotome, care being taken not to leave any loose fragments in the spinal canal.

The pillow is then removed from beneath the patient's abdomen and the table is straightened. This lessens the pressure in the extradural veins and at this time any cottonoid sponges which are still in the wound are removed. Usually it will be found that there is no further bleeding. However, if bleeding continues the bleeding point is packed off with a cottonoid sponge and a small bit of muscle is cut from the side of the wound, crushed with forceps, and held against the bleeding point until the hemorrhage is controlled and the wound is closed with this muscle in place.

The nerve root is again retracted and the disc inspected. If the change in position has caused any more disc material to appear in the

cavity this is removed. The wound is then sprinkled with sulfonamide powder and closed in layers, using chromic and plain catgut for the deeper tissues and cotton for the skin. A rather small dressing is applied and the patient is placed on an ordinary bed and permitted to lie in whatever position is most comfortable. The skin sutures are removed on the seventh day and he is allowed up on about the twelfth day and permitted to leave the hospital. He is advised to increase his activities gradually and to avoid strain on the back for at least eight weeks.

Spinal Fusion.—If spinal fusion is decided upon, this is done as follows: The deeper tissues on the opposite side and an area over the posterior part of the crest of the ilium are infiltrated with novocain; the lamina and articular facets on the opposite side are exposed subperiosteally. The interspinous ligaments and the periosteum are completely removed from the opposing borders of the spinous processes and lamina and with a rongeur a small notch of bone is pinched out from the opposing borders of the bases of the spinous processes. Small slivers of bone are raised, but not detached from the laminae and posterior surface of the sacrum, and the cartilage is removed from the articular facets.

Through a curved incision over the crest the posterior surface of the ilium is exposed, a rectangle about 1 by $1\frac{1}{2}$ inches is outlined with an osteotome, and the slab of cortex with some of the underlying cancellous bone is excised. A small notch is pinched out of each of the longer sides of this rectangle of bone with a rongeur, the spinous processes are separated by flexing the lumbar spine, and the graft is inserted between them, the notches in the graft fitting in those in the spinous processes. As the lumbar spine is extended the graft is held firmly in place and closely applied to the roughened lamina and sacrum, covering the defect left by the removal of the ligamentum flavum. Additional cancellous bone may then be obtained from the ilium, placed where indicated, and the wound closed. This method results in a rapid fusion and the patient remains in bed without immobilization for three weeks. He then may be gotten up with a wide lumbosacral belt and may discard all support in about three months (Fig. 2). It is similar to the operations described by Breck and Basom² and Bosworth.³

Postoperative Course.—As a rule, the postoperative course is uneventful. An occasional patient has difficulty in voiding for a few days after the operation and catheterization may be necessary. A few patients convalesce slowly and require about three weeks' hospitalization. About 20 per cent of the patients complain of numbness in the side of the foot, which has sometimes persisted for several months. Absence or diminution of the ankle jerk on the affected side has persisted in several patients. This may be due to the novocain, to traction on the nerve root, or to preoperative damage to the nerve root by the protruding disc.

In a series of 120 consecutive operations for ruptured intervertebral discs there were three hematomas which were evacuated, two mild wound infections, and one severe wound infection. In the severe infection the patient developed a staphylococcus septicemia. In this patient the wound healed normally, the sutures were removed, and there was no evidence of local infection until the tenth postoperative day, but the temperature rose on the third postoperative day and the septicemia was



Fig 2—Postoperative lumbosacral fusion by using slab graft from ilium

apparent a few days later. It is possible that this unusual course was due to the local sulfonamide in the wound. In spite of large amounts of penicillin the septicemia pursued a rapidly fatal course. The autopsy revealed no localized lesions except the wound and there was no evidence of meningitis, in spite of the fact that the dura had been torn slightly when it was dissected free from the protruded disc.

DISCUSSION

The results of the operation in my hands have not been as uniformly successful as I would wish. Some of my patients who have had definite discs removed are still complaining of pain and disability. One of these was re-operated and as no cause for the pain was found the spine was fused, but the pain has persisted. In two instances where a primary bone chip and Hibbs fusion was done at the time of the removal of the disc, reoperation with removal of the fused area on the affected side has resulted in complete relief in one patient and partial relief in the other, although nothing was found at either operation to explain the pain. Likewise, some patients in whom no pathology was found at the operation have been free from pain after the operation.

The explanation of failure to cure is not known. Undoubtedly, some of the failures are due to protrusion of a second disc which was not removed at the operation. Others are due to recurrence of protrusion of an incompletely removed disc. In others there seems to be a persisting neuritis in the involved nerve roots. In one patient treatment with deep x-ray therapy has been followed by partial relief.

In some cases compensation is a factor and operation in these cases is to be avoided unless the history and clinical findings are clear cut and the patient appears to be anxious to get well and return to work. It is more satisfactory to have the case settled and then let the patient decide whether or not he wants to be operated upon. It is very difficult to return these patients to a job involving manual labor as long as they are drawing compensation and trying to settle their claim. Much the same is true of enlisted men in the Armed Forces. Elective surgery on the enlisted man should be undertaken only after a thorough trial of conservative treatment and in most instances it is wise to place these men on limited service immediately and continue the conservative treatment while they are doing duty.

I do not believe that spinal fusion will result in relief of symptoms in many of the patients who have not been relieved by removal of the disc. I am now fusing fewer spines than I did two years ago and am no longer using bone chips over the open spinal canal after the ligamentum flavum has been removed, but prefer the notched plate graft described. I am not sure that the unusually thorough curettement used by Dandy¹ will result in fusion. The occurrence of Schmorl's nodes indicates that the interior of the vertebral body is very unstable if the osteocartilaginous plate is perforated or removed.

At present I know of no acceptable indications for fusion of the intact spine after the removal of a protruding intervertebral disc. In some clinics the spine is fused if a congenital anomaly is present, in others the spine is fused if the lumbosacral joints are considered to be unstable, and in others the spine is fused if hypertrophic changes are present. None of these are acceptable reasons for fusion. At present I do not

fuse the spine if a definitely abnormal disc has been removed, but reserve this operation for those patients with long-continued, chronic backache in whom the x-rays reveal a collapsed disc and in whom no pressure on the nerve roots is found and relieved at the operation. If spondylolischisis or spondylolisthesis is present, fusion is indicated if operation is indicated, but in these cases the spine is not intact and exploration of the disc is rarely indicated if the pain is relieved by rest in bed.

From what has been written here it is evident that we should continue to treat low back pain, with or without sciatica, conservatively and that we should reserve operative removal of the discs for those patients who do not respond to conservative treatment. It is also to be noted that the operation in its present state of evolution is not a completely satisfactory answer to the problem, but the same is true of most operations. In relatively few surgical conditions do we expect to cure 100 per cent of the patients of all of their symptoms by operation. When viewed in this light removal of a ruptured intervertebral disc is a sound surgical procedure if the cases are properly selected. When patients are not relieved by the operation, or when symptoms recur, the conservative treatment along the lines described should be used and they should not be operated upon until this has failed to give relief.

REFERENCES

1. Dandy, W. E.: Newer Aspects of Ruptured Intervertebral Discs, *Ann. Surg.* 119: 481, 1944.
2. Breck, L. W., and Basom, W. C.: Flexion Treatment of Low Back Pain, *J. Bone & Joint Surg.* 28: 58, 1943.
3. Bosworth, D. M.: Clothespin or Inclusion Graft for Spondylolisthesis or Laminar Defects of Lumbar Spine, *Surg., Gynec. & Obst.* 75: 593, 1942.

CRANIOPLASTY WITH TANTALUM PLATE

REPORT OF EIGHT CASES

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TANTALUM is a biologically inert metal in the sense that it does not corrode and does not irritate living tissue. It is the seventy-third element in the periodic table. Ekeberg, who discovered it in 1802, gave it its name because he found it tantalizing when he attempted to dissolve it in mineral acids. Despite its discovery over a century ago, it was not until 1940 that this metal was introduced for surgical use.¹ For the surgeon, particularly the neurosurgeon, it may prove to be the ideal metal, but sufficient reports of its clinical use have not yet been made to justify this conclusion.

Pudenz and Odom,² in the experimental study to develop a material which would prevent meningeocerebral adhesions, reported absence of foreign body reaction and failure of development of adhesions between the cerebral and meningeal surfaces following the prolonged application of tantalum foil to the surface of the brain of cats. Pudenz³ subsequently made an experimental comparison of the reaction induced by tantalum and silver clips implanted in the brain and meninges of cats. He found that the tantalum clips provoked minimal reaction, in contrast to considerable leucocytic infiltration following implantation of silver clips. Later, Pudenz⁴ demonstrated the inertness of tantalum in animal tissue when he used tantalum plates to repair cranial defects in cats. Following removal of the plates with the surrounding tissue in one block, the plates were found to be enveloped in a delicate membrane which was adherent to the dura but easily separated from it, and the metal was found to be unchanged. There was neither inflammatory reaction nor osteoplastic inhibition at the edges of the defects and the capsules surrounding the plates were not of a progressive nature.

Since this work of Burke, Pudenz, and Odom, a number of neurosurgeons have been using tantalum to repair cranial defects. Fulcher⁵ recently reported excellent results in one case. Penfield, Cone, and Spurling, in personal communications to Pudenz, have stated that they have used tantalum plates in the repair of cranial defects with uniformly excellent results. From personal communications we have learned that Army neurosurgeons are using tantalum almost exclusively for the repair of cranial defects. It is believed that 500 cases of cranioplasty with tantalum could now be assembled.

Received for publication, July 28, 1944.

Tantalum* is manufactured in the form of sheets, foil, ribbon, wire, screws, and orthopedic plates. Because of its widespread use in the manufacture of war material, it has only recently been released in limited quantity to civilian surgeons.

Among the physical properties of this metal which make it of surgical value are strength and malleability. In its annealed state it is ductile and can be drawn into fine wire, which makes an excellent suture material.

PREPARATION OF PLATES AND OPERATIVE TECHNIQUE

A tantalum plate can be laid on the skull so as to cover the defect completely (onlay method, Fig. 1, *A*) or it can be trimmed to the exact size and shape of the defect and inserted (inlay method, Fig. 1, *B*). For cranioplasty with the onlay technique a plate .0125 inches or less in thickness is desirable. The location and configuration of the defect in the skull should be noted. A sheet of metal should be cut to the approximate size and shape with tinsmith's shears and hammered to the correct curvature with a ball peen hammer. A skull should be available in the workshop as a guide. Many perforations should be made

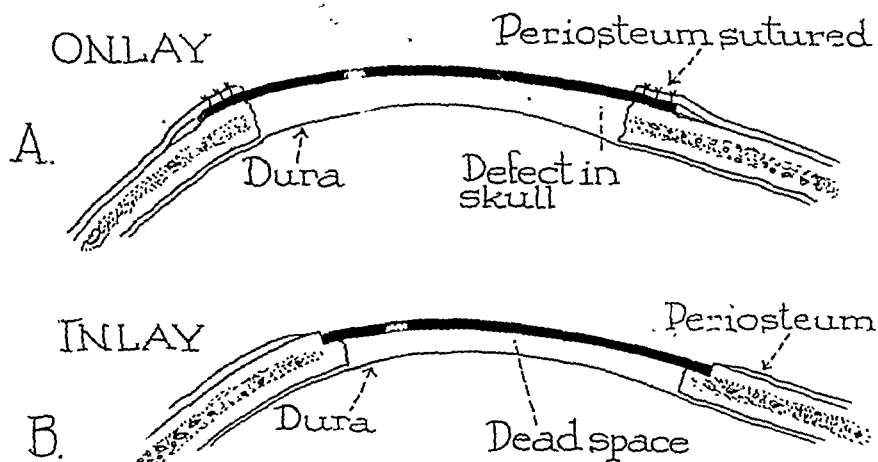


Fig. 1.—A, Onlay technique; B, inlay technique.

in the plate with a drill to facilitate suturing or wiring and provide for escape of cerebrospinal fluid and blood into the subgaleal space from which it may be absorbed or aspirated. Some observers state that a perforated plate is not desirable because the scalp is more apt to become attached to it.

At operation, under local or general anesthesia, the defect in the skull is exposed by reflecting a flap of scalp. The periosteum is retracted from the edge of the defect in the skull so that the metal plate can be laid in direct contact with the bone. If the plate is found to be too large, necessary alterations should be made with the shears. The plate

*Tantalum Defense Corporation, North Chicago, Ill.

should, of course, be somewhat larger than the defect in the skull. It is important that the edge of the plate be in contact with the surface of the skull if a palpable ridge is to be avoided. The periosteum is brought over the plate and sutured with cotton, silk, or tantalum. In case of an inadequate periosteum it is important to fasten the plate to drill holes in the skull by means of tantalum wire. A plate can also be secured to the skull with two or three tantalum screws. Migration of insecurely fastened plates has occurred. The scalp is closed in two layers with interrupted sutures of silk or cotton and a pressure dressing is applied.

Inlay Method.—The inlay method of cranioplasty with tantalum involves the making of positive and negative casts of the defect in the skull. The plate is then swaged into the desired shape. This method was demonstrated at the meeting of the American Academy of Neurological Surgery in Battle Creek in 1943 by Mayfield and Levitch and is presented in a motion picture made at the Walter Reed General Hospital. With a few special instruments the outer table of the skull is chiseled away around the entire periphery of the defect. This permits the plate to rest on the ledge formed by the inner table. The metal plate is flush with the surface of the cranium (Fig. 1B). The plate is firmly secured by driving several triangular tantalum wedges into the bone, much as a glazer secures the windowpane. If the cranial defect is on the forehead, the inlay method is especially desirable, as a slightly better cosmetic effect can be obtained.

The inlay technique is an excellent one but is not universally suitable because it is time consuming and expensive even though the material and equipment are available in dental laboratories. We have not used this technique and are reasonably well satisfied with the simpler one already described.

RESULTS

We have used tantalum plate to repair cranial defects in eight cases. Two patients had depressed fractures, recently healed. Three had old depressed fractures, complicated by convulsive seizures. Also included was a large defect of the frontal bone following osteomyelitis, which had been "cured" by surgical treatment. A case of parasagittal meningioma with exostosis at the vertex in which a large operative defect was repaired at the time of operation is presented. Another patient presented a compound fracture of the frontal bone with loss of the frontal sinus and roof of the orbit; there was displacement of the globe with diplopia. This case presented a difficult prosthetic problem because of the peculiar shape of the plate to be made.

In this small group of cases there were two complete failures. One patient (Case 4) returned to the hospital one year after operation on the frontal bone for osteomyelitis. A plate was applied but this was promptly followed by infection, whether because of defective aseptic

technique or as the result of stirring up latent infection by too early repair, we cannot say. In another patient (Case 1) the plate had to be removed one year later because of infection. This is difficult to explain, as there were complicating factors including the fact that the plate was inserted into a potentially infected wound. A more likely explanation is that the edge of the plate may have been elevated from the skull at one point with resulting erosion of the scalp. In the other six cases the plates have remained in place after periods ranging from two and one-half to fifteen months. In one of these (Case 6) the results are not entirely satisfactory because the patient complains of an intermittently sore scalp over the plate. This suggests the possibility that the plate may become hot when the patient is working in the sun. There is an untraceable rumor that cranial plates of tantalum absorb heat if the patient is exposed to sunlight or diathermy. The authenticity of this statement should be established before too extensive use of this metal is made.

CASE REPORTS

CASE 1.—I. L., a Negro, aged 47 years, was admitted to Charity Hospital in New Orleans, Jan. 22, 1943. Five days previously he was hit over the head by a car crank and was unconscious for two days. At the time of admission he was conscious and able to walk but was aphasic. Otherwise, neurologic examination gave negative results. On the left side of the head there was a scalp wound which had been closed by three sutures and was healing by first intention. Deep to this wound an osseous depression was felt. Roentgenograms revealed a depressed fracture of the skull involving the parietal and temporal bones. Feb. 2, 1943, eleven days after the injury, a small scalp flap was reflected downward over the ear. A trephine was made near the edge of the depressed fracture and all of the fragments were removed. One fragment had been driven through the dura. When this fragment was removed, an underlying artery on the surface of the brain began to bleed. In order to control this hemorrhage the dura was opened widely and then closed with interrupted cotton sutures. A perforated tantalum plate, which had already been prepared, was trimmed to the proper size and laid over the defect. It was fastened to the periosteum with several cotton sutures. Convalescence was complicated by bronchopneumonia which had cleared up by Feb. 6, 1943. The patient was discharged from the hospital Feb. 12, 1943. At re-examination, March 19, 1943, the wound had healed and the aphasia had completely disappeared. The patient had no complaints. In May, 1944, the patient returned to the hospital because the tissues around the plate had become infected. Inspection disclosed an ulcer of the scalp 2 cm. in diameter through which the plate could be seen. Pus escaped from the opening and the entire scalp flap was swollen. The plate was removed a few days later and the infection promptly subsided.

CASE 2.—E. L., a white man, aged 21 years, was admitted to Touro Infirmary Feb. 26, 1943, because of multiple contusions and lacerations caused by a fall. Two lacerations of the scalp had been sutured at a first-aid station; healing by first intention resulted. Roentgenograms of the skull made some days later showed a comminuted depressed fracture of the frontal bone. This proved to underlie one of the healed lacerations. At operation, March 12, 1943, two weeks after the injury, a small scalp flap was reflected to expose a depressed fracture about the size of a quarter. A trephine was made adjacent to this and the depressed fragments were removed. The inner table was more extensively fractured than the

outer table. The dura was intact. A small amount of organized blood clot was also removed. A perforated tantalum plate, which had been prepared in advance, was laid over the skull defect and fastened to the periosteum with one cotton suture. The scalp was closed in two layers with cotton and a pressure bandage was applied. Convalescence was uneventful and the patient was discharged from the hospital on the eighth postoperative day. June 25, 1941, fifteen months after operation, the patient wrote that he was well and completely satisfied with the plate.

CASE 3.—F. B., a Negro man, aged 29 years, was admitted to Charity Hospital in New Orleans, June 4, 1943, because of jacksonian convulsions on the right side. He sustained a simple depressed fracture of the skull in October, 1940. In October, 1941, he began having frequent convulsions. There was a palpable depression of the left parietal bone. June 24, 1943, the skull was exposed, a trephine opening was



Fig. 2 (Case 3).—Postoperative view showing plate wired in place over defect.

made, and the depressed portion of the skull removed. One fragment of bone had penetrated the dura. The dural opening was enlarged to permit removal of this fragment; the brain appeared normal. A previously fashioned tantalum plate was cut to the correct size and wired in place over the defect (Fig. 2). There were no postoperative convulsions. The patient was discharged from the hospital, July 7, 1943, with instructions to take anticonvulsive medication for one year. He was drowned while swimming in February, 1944.

CASE 4.—J. H., a Negro boy, aged 16 years, came to Charity Hospital in New Orleans, June 28, 1943, because of a defect in the frontal bone. July 14, 1942, he was operated on for extensive osteomyelitis;* all of the infected bone, including

*Operation by Dr. Guy Odom.

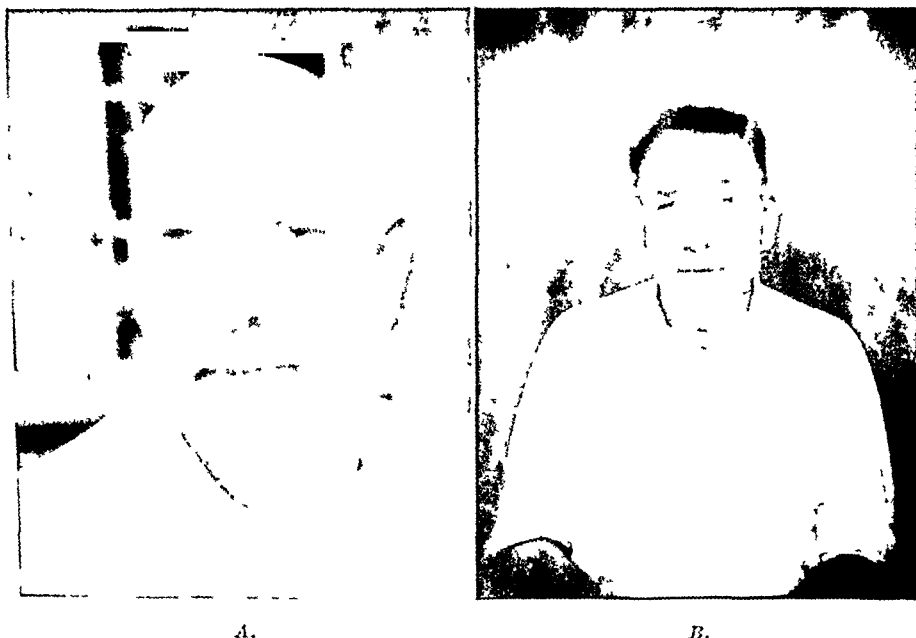


Fig. 3 (Case 5) — *A*, Preoperative photograph showing loss of supra-orbital ridge *B*, postoperative photograph showing restoration of the supra-orbital ridge.



Fig 4A (Case 5).—Lateral view showing reconstruction of roof of orbit and supra-orbital ridge.

most of the walls of the frontal sinus, was removed. Following an uneventful convalescence he was discharged from the hospital, Aug. 5, 1942. Roentgenologic examination, July 29, 1942, showed an extensive defect in the skull but no evidence of sequestra or infection. He returned to the hospital one year later to have this defect repaired. July 22, 1943, an incision was made through the scar of the old hypophyseal type flap and the scalp reflected. After adequate hemostasis had been obtained, a previously shaped tantalum plate was laid over the defect. It fitted so snugly that sutures were not deemed necessary. The flap was closed in one layer with cotton sutures. July 24, 1943, there were 10 c.c. of serosanguineous fluid aspirated from beneath the flap. July 28, 1943, similar material, 50 c.c., was withdrawn. Culture showed *Staphylococcus pyogenes aureus*. There was little fever or pain. Attempts to save the plate were eventually abandoned and it was removed on Aug. 20, 1943. The wound was closed in one layer, and a rubber drain left in place. Convalescence was without incident and the patient was discharged, Aug. 23, 1943.

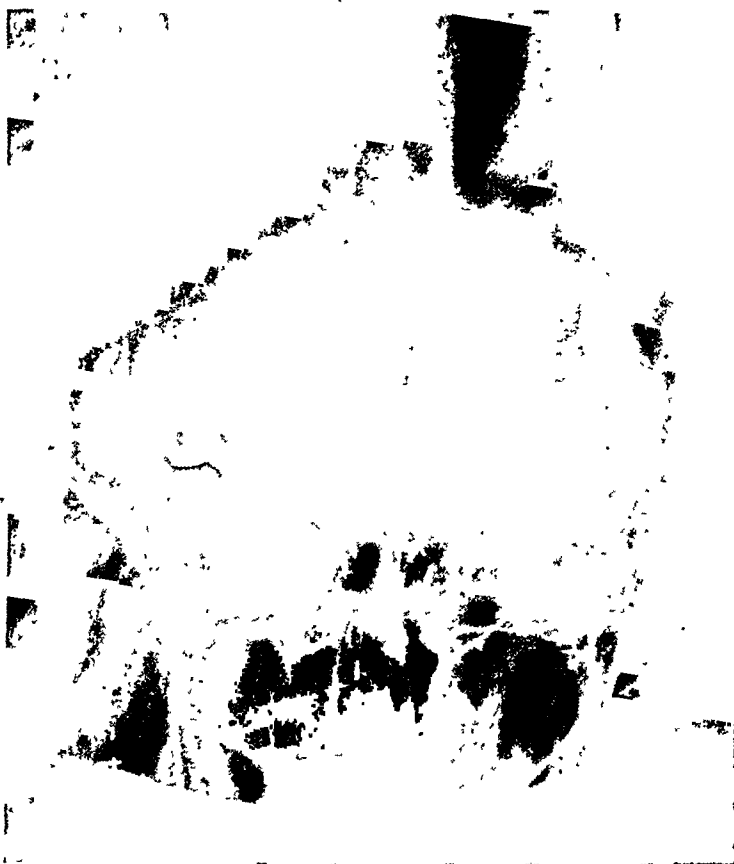


Fig. 4B (Case 5)—Postero-anterior view showing reconstruction of portion of frontal bone and supra-orbital ridge; the portion of the plate which forms the roof of the orbit is seen in Fig. 4A.

CASE 5.—J. P., a 51-year-old white man, was admitted to Touro Infirmary, Aug. 2, 1943. Nine months previously he had sustained a compound fracture of the right frontal bone which had healed following débridement. The frontal sinus, supra-orbital ridge, and part of the roof of the orbit were missing; this produced displacement of the eye and diplopia (Fig. 3A). No puls

complained of numbness of the forehead, pain in the right side of the forehead, and double vision. A coronal incision was made just behind the hairline of the forehead and the scalp reflected over the eyes and nose. Sharp dissection was required to separate the scalp from the dura; no difficulty was encountered in separating the dura from the periorbital. A previously fashioned tantalum plate was trimmed to the exact size with tin shears and slipped into position to replace the missing supra-orbital ridge and the roof of the orbit (Figs. 4A and 4B). Following an uneventful postoperative course the patient was discharged from the hospital, Aug. 18, 1943. The original scar was repaired some months later. Re-examination in February, 1944, showed a satisfactory cosmetic result (Fig. 3B) and practically complete correction of the diplopia. However, the frontal pain still persisted.



Fig. 5A (Case 7).—Preoperative view showing exostosis overlying parasagittal meningioma.

CASE 6.—E. C., a white man, aged 43 years, was admitted to Charity Hospital in New Orleans, Aug. 16, 1943. Twenty years before, he received a gunshot wound in the left temple from which he recovered except for mild aphasia. He was well until December, 1942, when he began to have headaches originating at the left side of the nose. Two months before admission he had a convulsion during which he was unconscious. Two weeks before he came to the hospital, he had another convulsion. Examination revealed the scar of an old wound in the left temporal region with a palpable defect at the same site. The scalp was adherent to the underlying tissues. Roentgenograms revealed the presence of a cranial defect and

numerous shotgun pellets in the soft tissues, some outside and some just inside the cranial cavity. Aug. 26 1943, a scalp flap was reflected downward over the ear. The soft tissues covering the defect were dissected from the dura and the defect in the skull was enlarged to two inches in diameter. The exposed dura was excised with difficulty. Many adhesions between the brain and dura and many large vessels were encountered. A scarred area of brain one and one half inches in diameter was noted with cystic spaces near the surface. Nothing was done to the scar because of its location for fear of making the aphasia worse. A previously shaped tantalum plate was cut to the correct size, laid over the defect, and wired into place. The patient was given $1\frac{1}{2}$ gr. of sodium, 5,5-diphenyl hydantoinate (dilatin sodium) three times a day. Convalescence was uneventful. He had no convulsions prior to discharge from the hospital, Sept. 8, 1943.

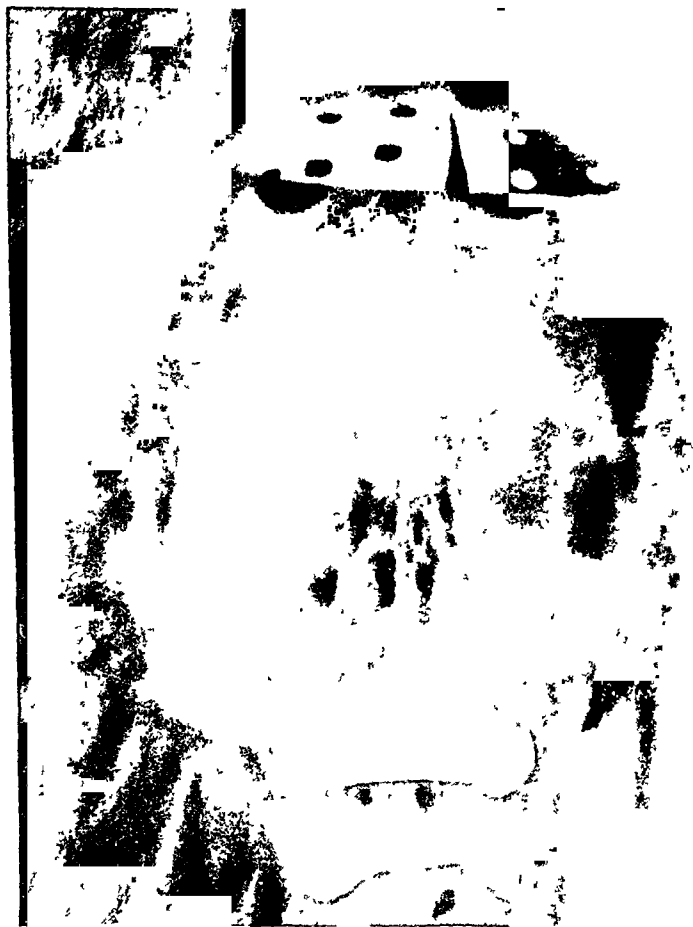


Fig. 5B (Case 7).—Postoperative view showing large tantalum plate covering operative defect.

April 26, 1944, eight months after operation, the patient wrote that he was free of convulsions but that he still suffered from the headache which had begun in December, 1942. The pain is apparently brought on by working two or three consecutive days on his farm. This point, together with the fact that the scalp over the plate becomes sore, suggests the possibility that the plate becomes heated. On the other hand, headache was a major complaint before insertion of the plate.

CASE 7.—S. P., a white woman, aged 62 years, was admitted to Touro Infirmary, Oct. 20, 1943, because of exostosis of the skull (Fig. 5A) accompanied by other evidence of a parasagittal meningioma. Oct. 26, 1943, a large U-shaped flap of scalp was reflected so that the hyperostosis and a margin of normal skull could be removed in one piece. A stalk of neoplastic tissue which connected the hyperostosis with a large parasagittal meningioma was broken with the finger. The dura was opened on each side of the sagittal sinus. On the left was a small meningioma which proved to be an extension (through the sinus) of the larger tumor. Both tumors, the adjacent dura, and the intervening sinus and falx were removed in one piece. The depressed portion of the right hemisphere promptly expanded. The cut edge of the dura was sutured to the periosteum around the entire periphery of the defect in the skull. A previously prepared tantalum plate was laid in place over the defect (Fig. 5B), the scalp was closed with cotton sutures, and a pressure dressing was applied.

At the time of re-examination, May 2, 1944, the patient was found to be in good health. She had regained the ability to walk, her personality had returned to normal, and the convulsions had ceased. At two places the edge of the plate could be palpated and the patient complained of tenderness. It was realized at the time of insertion that this was not a perfectly fitting plate.

CASE 8.—J. M. R., a white man, aged 56 years, was admitted to Touro Infirmary, Jan. 31, 1944, because of convulsive seizures and headaches. He had sustained a penetrating wound on the left side of the head at the age of 5 years. From the age of 20 until the time of a craniectomy at the age of 31 he experienced frequent severe convulsions with loss of consciousness. This operation (craniectomy at the site of the old wound and possibly excision of a meningocerebral cicatrix) was followed by temporary hemiplegia but it greatly diminished the frequency and severity of the convulsions. The patient had also had a prostatic operation, open drainage for empyema, and nephropathy.

Examination disclosed a cranial defect on the left side near the midline and about one inch back of the hairline. An encephalogram, made Feb. 1, 1944, showed moderate dilation of both lateral ventricles, the left being larger. There was slight tenting of the portion of the ventricle nearest the cranial defect. At operation, Feb. 5, 1944, the cranial defect measured 3 by 5 cm.; it extended to the midline. The opening in the skull was enlarged with rongeurs. The dura, which was firmly adherent to the brain, was excised to the margin of the sagittal sinus, dissected free, and discarded. The sinus was inadvertently opened at one point and had to be closed with a suture. There were no adhesions between the medial surface of the hemisphere and the falx. The brain scar was smaller than a dime and nothing was done to it, although it was probably far enough forward to have been removed without causing motor symptoms. A tantalum plate was laid over the defect and fastened in place with two tantalum wires. The periosteum and scalp were closed in layers. Feb. 10, 1944, some fluid, which had accumulated under the scalp, was aspirated with a needle and syringe. No convulsions occurred. The patient was discharged from the hospital, Feb. 15, 1944, with instructions to take sodium, 5,5-diphenyl hydantoinate (dilantin sodium) for one year. He was asked to come back for removal of the brain scar if the convulsions returned.

April 19, 1944, two and one-half months after operation, the patient wrote that he was working (watch repairing) and free of all head pain. He had experienced two light convulsive seizures without loss of consciousness and as a result had given up dilantin and gone back to taking phenobarbital, $\frac{3}{4}$ gr. three times daily.

SUMMARY

The properties of tantalum which make it a suitable metal for repairing cranial defects are enumerated and experimental evidence to

support this contention is cited. A technique of preparing tantalum plates for cranial defects is described. Eight cases in which tantalum plates were used to repair old or new cranial defects are reported. Satisfactory results were obtained in all but two instances, a case of osteomyelitis of the skull, which immediately became infected, and a compound fracture of the skull, not debrided at the time of injury, which became infected one year after cranioplasty.

REFERENCES

1. Burke, G. L.: The Corrosion of Metals in Tissues and an Introduction to Tantalum, *Canad. M. A. J.* 43: 125-128, 1940.
2. Pudenz, R. H., and Odom, G. L.: Meningocerebral Adhesions; an Experimental Study of the Effect of Human Amniotic Membrane, Amnioplastin, Beef Allantoic Membrane, Cargile Membrane, Tantalum Foil, and Polyvinyl Alcohol Films, *SURGERY* 12: 318-344, 1942.
3. Pudenz, R. H.: The Use of Tantalum Clips for Hemostasis in Neurosurgery, *SURGERY* 12: 791-797, 1942.
4. Pudenz, R. H.: The Repair of Cranial Defects With Tantalum; an Experimental Study, *J. A. M. A.* 121: 478-481, 1943.
5. Fulcher, O. H.: Tantalum as a Metallic Implant to Repair Cranial Defects, *J. A. M. A.* 121: 931-933, 1943.

Editorial

Thrombo-Embolism

OPERATIVE treatment in all fields of surgical endeavor has been steadily improved due, in part, to the analytic study of complications and end results. It has been demonstrated that while the primary procedure might be correctly chosen and meticulously carried out, a fatal result was frequently due to secondary involvement of other organs and vital physiologic functions by disease processes initiated by trauma of operation, anesthesia, and other mechanics of treatment and convalescence. Pulmonary complications following operation have gradually been sorted out from the original ether pneumonia until a fairly satisfactory classification of their causes is now available. Aside from the activation of residual disease of bronchial tree and lungs by anesthetics, atelectasis as an important complication has been recognized. The frequency of occurrence and methods of diagnosis of this acute pulmonary complication are common knowledge and techniques for its prevention and treatment are well established.

It has long been known that pulmonary embolism was another not infrequent and often fatal complication of any operation. Many misconceptions pervaded surgical thought over the course of years concerning the origin of the thrombosis that initiated these emboli. Studies by many observers during recent years have finally clarified this problem and it is increasingly evident that most pulmonary emboli following operation have their origin in thrombi formed in the veins of the foot, leg, and thigh. It was originally thought that thrombosis in these veins started in the upper part of this venous system, in the femoral and lower iliac veins. Further studies by pathologists and clinicians have shown that thrombosis usually starts below the knee, frequently in the veins of the foot. From such a start, the process may advance to noninflammatory masses of thrombi in the femoral or iliac vessels called phlebothrombosis or to an obstructive inflammatory lesion known as thrombophlebitis.

The further local progress and distant spread of portions of the thrombi are variable but of important consequence. The etiologic factors favoring the origin of thrombosis have been widely studied and the importance of the many factors involved have been individually emphasized. Abnormalities in the clotting mechanism of the blood, anatomic and pathologic abnormality in the vein, and physiologic alterations associated with posture and lack of normal activity have all been mentioned frequently as primary or contributing factors. Both chemical and mechanical methods of prevention of thrombosis have their exponents.

Treatment ranges from bold operations to remove pulmonary emboli after their lodgment, to ligation of vein, aspiration of thrombus, and sympathetic block, to chemical methods of altering clotting time. Just as it is often difficult during a political campaign to keep before one the main issue, despite one's prejudices and the claims of opposing factions, so now, we as surgeons are faced with the difficulty of judging impartially the merits of the forms of treatment and the methods of prevention and treatment now advocated in thrombo-embolism arising in the peripheral venous system. The characteristic signs and symptoms of thrombosis in the peripheral venous system, many of the predisposing factors involved, and the characteristic manifestations of distant embolism calling the attention of the unwary surgeon to the presence of a frequently unsuspected thrombosis, have all been given recent prominence in surgical literature. One may safely say that frequent inspection of the lower extremity should become a routine in the care of all patients having undergone an operation. The recognition of early thrombosis is a necessity to the proper treatment, no matter what type of therapy may be chosen.

A state of indecision always arises when more than one form of therapy in prevention and treatment is available. Medical progress is based on the amassed statistics of groups or individuals vigorously championing one or the other form of treatment. The problem of thrombo-embolism is at present in this state. Statistical studies are being compiled in favor of ligation of large veins of the extremities or of the trunk to prevent distant emboli and further progression of thrombosis in these veins. With a similar end in view, enthusiasts for anti-coagulant therapy in this same group of patients are presenting a formidable showing in the current literature. There is no doubt but that sympathetic block overcomes the vasospasm and thereby aids recovery when such vasoconstriction is present. This state of affairs in which different methods of treatment have merits receives our cordial and enthusiastic encouragement. Truth of deduction can come only from intensive studies of all methods. We are no longer ignorant of the source of the majority of pulmonary emboli. The conservative methods of prevention by encouraging normal physiologic forces of venous flow by exercises and voluntary activity in bed and early post-operative mobilization after operation can elicit little antagonism. What then shall we do for those patients who, despite conservative preventive measures, develop evidence of peripheral venous thrombosis? This question will be answered on the basis of the comparative statistics compiled from the studies of those now at work in the field.

How can we judge the merits of the available forms of treatment? If one keeps in mind certain precepts one may be able to judge well for his patients. The formation and propagation of thrombi in the vascular tree must be prevented by promoting normal physiologic proc-

esses; if the process is initiated it must be stopped. The measures used by the surgeon must be simple, readily available, and effective. The treatment of thrombo-embolism as a complication must neither affect adversely the primary disease nor interfere nor complicate the treatment which is essential to this disease. The morbidity and mortality associated with the accepted therapy must be minimal. When these criteria are fulfilled, the problem of thrombo-embolism will no longer be a problem. The primary fact of source is now known. It is possible to extend prophylactic methods universally. Its early recognition is dependent upon simple clinical examinations. The numerous investigators in the field of treatment are urged to continue along their divergent lines of research and therapy until the analyses of their efforts will give the final truth.

—*Frederick A. Collier, M.D.*

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Book Reviews

The Neurosurgical Patient: His Problems of Diagnosis and Care. By Carl W. Rand, M.D. Cloth. Pp. 576, with 121 illustrations. Springfield, Ill., 1944. Charles C Thomas, Publisher. \$4.

The growth of the field of neurosurgery from one concerned chiefly with attempts at removing neoplasms of the brain and spinal cord to one encompassing both anatomic and physiologic disorders of the nervous system at all levels is well illustrated by this volume by one of the Pacific Coast's leading neurosurgeons. In it, in addition to extensive discussions of the several varieties of brain and spinal cord tumors and of the near and remote effects of skull and spine injuries, one finds briefer consideration of the surgery of the peripheral and sympathetic nervous systems, of infections of the nervous system amenable to surgical management, and of such problems as the relief of malignant exophthalmos and spasmodic torticollis.

Each of the fifty-four chapters appears to be a more or less literal transcription of a clinical discussion presented by the author before groups of physicians or medical students. Each is introduced by a pertinent quotation from the older literature and the various problems discussed are accompanied by illustrations of patients from the author's experience. This, together with the conversational literary style, makes for easy, pleasant reading. However, the material is loosely organized and repetitions are frequent. Particularly annoying are the references to roentgenograms and diagrams which were displayed to the original audience but which are not reproduced for the reader. The details of surgical technique are not described.

The result is a book which will provide interesting reading for the physician curious about neurosurgery, but one which is not adequate as either a text or reference work.

SURGERY

VOL. 17

MARCH, 1945

No. 3

Original Communications

THE SIGNIFICANCE OF POLYMORPHONUCLEAR LEUCOCYTES IN GALL BLADDERS

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THIS study was undertaken in an attempt to determine, if possible, the significance of polymorphonuclear leucocytes in the walls of thin-walled, noncalculareous gall bladders. There is almost universal agreement that the presence of polymorphonuclear leucocytes seen in a histologic section of a gall bladder wall is an indication of inflammation. It was noted that, when the occasional thin-walled noncalculareous gall bladder was removed at operation, the histologic appearance of the gall bladder wall would reveal the presence of polymorphonuclear leucocytes; yet gross examination would show an intact glossy mucosa and a wall thin enough and free enough from thickening and edema that, when the specimen was held to the light, it would be translucent. In an appendix, a similar appearance would be interpreted as representing subacute appendicitis. The question which naturally arose was, Is this an inflammatory process or is this a normal physiologic process that is being observed? Going further, perhaps the presence of polymorphonuclear leucocytes in the walls of other surgically removed specimens, such as the so-called strawberry gall bladder or gall bladders containing stones, is not in itself an indication of inflammation if not associated with other gross findings such as edema, thickening, inflammation of the mucosa, or the microscopic picture of large numbers of polymorphonuclear leucocytes, lymphocytes, and edema.

There is no mention in the literature of polymorphonuclear leucocytes being present in gall bladders that are not the site of inflammation. Noble¹ noted the presence of polymorphonuclear leucocytes and lymphocytes in the gall bladders of infants less than 1 year of age examined at necropsy. He expressed the belief that these cells were not present in sufficient numbers to indicate an inflammatory process and he specu-

Received for publication, Aug. 7, 1944.

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lated as to whether or not many of these minimal cell reactions seen in gall bladders that had been removed surgically from adults really represented a pathologic process, but he went no further.

Boyd² mentioned the presence of polymorphonuclear leucocytes in the more acutely inflamed gall bladders, but not otherwise. Smith and Gault³ mentioned dilated capillaries with typical perivascular leucocytic infiltration in the acutely inflamed gall bladders but said nothing of their presence in chronic cholecystitis. McCartney,⁴ in his description of mild chronic cholecystitis, stated that "there is no gross convincing evidence of disease, but in some instances of this type the microscopic examination reveals definite accumulations in the serosa with occasional polymorphonuclear leucocytes in the wall." Here is a well-stated description of the problem. Is the microscopic picture here actually a pathologic process or is it a physiologic one? Admittedly there is no gross evidence of inflammation.

Mentzer⁵ found that in 75 per cent of 612 consecutive necropsy cases there were microscopic changes in the gall bladder, which he regarded as being pathologic. In these 612 necropsy cases, only 7.7 per cent of the deaths were due to gall bladder disease per se. The criterion for microscopic pathologic changes in the gall bladder was the presence of polymorphonuclear leucocytes or lymphocytic cells. On the basis of these findings, it would seem that there is a very high incidence of cholecystitis, or again, a physiologic function is being misinterpreted.

METHOD OF EXAMINATION

Twenty-five thin-walled noncalcareous gall bladders which had been surgically removed were selected for this study. These gall bladders grossly did not show any evidence of inflammation and, when they were held to the light, their walls were translucent. It was felt that, if the wall of the gall bladder was thin enough to transmit light in this manner, there could be very little fibrosis or edematous thickening.

For similar study and comparison, twenty-five so-called strawberry gall bladders and twenty-five gall bladders that contained stones were selected. In order that the iodized dye used in visualization of the gall bladder would not have to be considered as an irritative factor, twenty-five gall bladders were selected for which from the clinical history it was determined that an interval of at least twenty days had occurred between roentgenologic visualization and surgical removal of the gall bladder. Usually the interval between visualization and surgical removal is several days, and it was felt that concentration of the dye in the gall bladder might have some influence on the presence of the polymorphonuclear leucocytes in these gall bladders, because all of them were surgical specimens.

Ten gall bladders from dogs were examined to determine, if possible, whether a similar microscopic picture could be found. The dogs were

all in a state of excellent health, the gall bladders being obtained at the time heart-lung preparations were being made. It was felt that if polymorphonuclear leucocytes could be consistently found in the walls of these gall bladders, it would be difficult to conclude that these were examples of mild or subacute cholecystitis.

Ten gall bladders from fetuses between the ages of 3 and 5 months were also examined. This age was selected in order to obtain a gall bladder shortly after it had become a hollow organ but before it started to function as a gall bladder. Here it was felt that if the presence of polymorphonuclear leucocytes had to do with a metabolic function rather than an inflammatory process, one could postulate their absence from the recently developed nonfunctioning gall bladder of the fetus. All that remained to do was to prove this by microscopic examination.

Ten human appendices removed routinely during abdominal laparotomy and grossly not showing any evidence of inflammation were examined in a similar manner. Although the two organs have in common absorptive function, that of the appendix is immeasurably less than that of the gall bladder. If the polymorphonuclear leucocytes could not be demonstrated in the normally functioning appendix, this would tend to support the thesis that their presence in the gall bladder was metabolic and physiologic.

Lastly, a series of ten jejunums of dogs and a smaller number of noninflammatory human jejunums were examined with the thought of comparing the microscopic appearance of an organ of known highly absorptive function with that of the gall bladder, which is also known to have a definite absorptive function. The presence or absence of the polymorphonuclear leucocytes in the walls of the jejunum would be very important to support or discount the assertion of metabolic versus inflammatory function.

HISTOLOGY AND METHOD OF MICROSCOPIC EXAMINATION

Maximow and Bloom⁶ divided the wall of the gall bladder into four layers: (1) a mucous layer consisting of a surface epithelium and a lamina propria, (2) a layer of smooth muscle, (3) a perivascular connective tissue layer, and (4) a serous layer covering part of the organ.

For the purpose of examining each section conveniently and accurately, it was decided to divide the wall of the gall bladder into three layers. The epithelium to the smooth muscle was one layer, the muscular layer was the second, and the tissue from the muscular layer, to and including the serosa, was the third layer.

Each of the three layers was then examined for the presence of polymorphonuclear leucocytes in the following positions: (1) in and around capillaries, (2) in and around lymphatics, and (3) in the tissue spaces. The type of polymorphonuclear leucocyte present was not determined in general, although eosinophiles were noted because of their consistent presence in the walls of the appendix.

Lymphatics could not be positively identified, but vessels whose walls consisted only of endothelial cells and whose lumina did not contain any erythrocytes were assumed to be lymphatics. In general, what was considered most important was the presence or absence of polymorphonuclear leucocytes regardless of location, except, of course, their association in normally accepted numbers mixed with erythrocytes in blood vessels. The same scheme was followed in examining microscopically the slides of jejunal and appendical tissue.

For simplification, the number of polymorphonuclear leucocytes in a single low-power, dry, microscopic field in any of the three layers or any of the three locations was classified numerically as occasional, few, and many. An occasional polymorphonuclear leucocyte would indicate one to three per low-power dry field, a few would indicate four to eight per low-power dry field, and many would indicate eight or more per low-power, dry, microscopic field.

HISTOPATHOLOGY

In the thin-walled noncalcareous gall bladders, polymorphonuclear leucocytes were found to be present in every section (Table I). In twelve of the microscopic sections many polymorphonuclear leucocytes were found to be present in at least one of the layers of the gall bladder. In eleven of the cases there were only a few, and in two cases only an occasional polymorphonuclear leucocyte was present. Many times polymorphonuclear leucocytes were present in one of the layers but in none of the others in the same histologic section (Fig. 1).

A similar microscopic picture was found in the strawberry gall bladders except that, in those sections in which many polymorphonuclear leucocytes were present, the total number present in a single field was greater than was found in the sections of thin-walled noncalcareous gall bladders. In eleven of these gall bladders there were many polymorphonuclear leucocytes, in nine there were a few, and in five there was only an occasional polymorphonuclear leucocyte (Fig. 2).

TABLE I
POLYMORPHONUCLEAR LEUCOCYTES IN THE WALL OF GALL BLADDERS

	SPECIMENS	CONTAINING LEUCOCYTES		
		MANY	FEW	OCCASIONAL
Thin-walled noncalcareous*	25	12	11	2
Strawberry gall bladder*	25	11	9	5
Gall bladders containing stones*	25	9	12	4
No dye*	25	6	12	7
Dog gall bladder	10	2	5	3
Fetal gall bladder	10	0	0	0
Dog jejunum	10	2	2	5

*All these gall bladders were surgically removed.

Nine of the gall bladders that contained stones had many polymorphonuclear leucocytes in the wall, twelve had a few, and four had an

occasional polymorphonuclear leucocyte. The walls of all these gall bladders were thickened and fibrotic microscopically (Fig. 3). Grossly, none of the calcareous gall bladders showed evidence of acute inflammation.

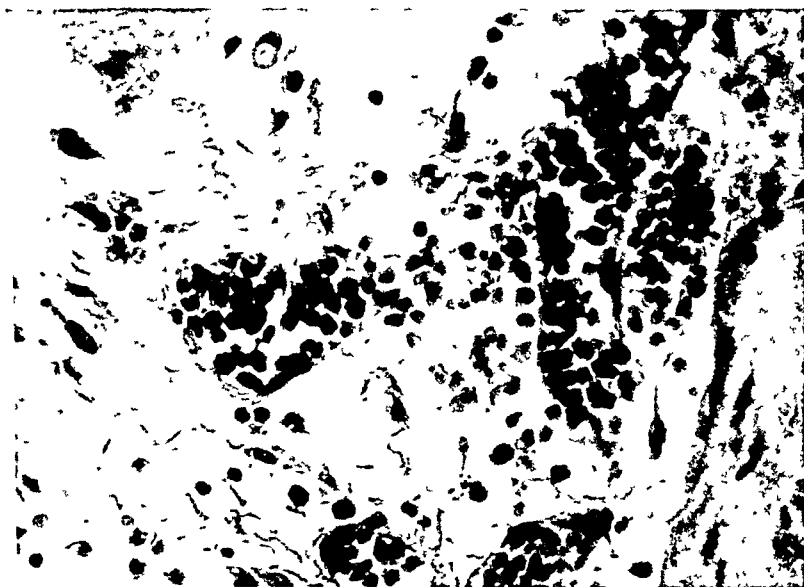


Fig. 1.—Wall of thin-walled noncalcareous gall bladder. Note the presence of occasional intracapillary polymorphonuclear leucocytes (hematoxylin and eosin $\times 435$).

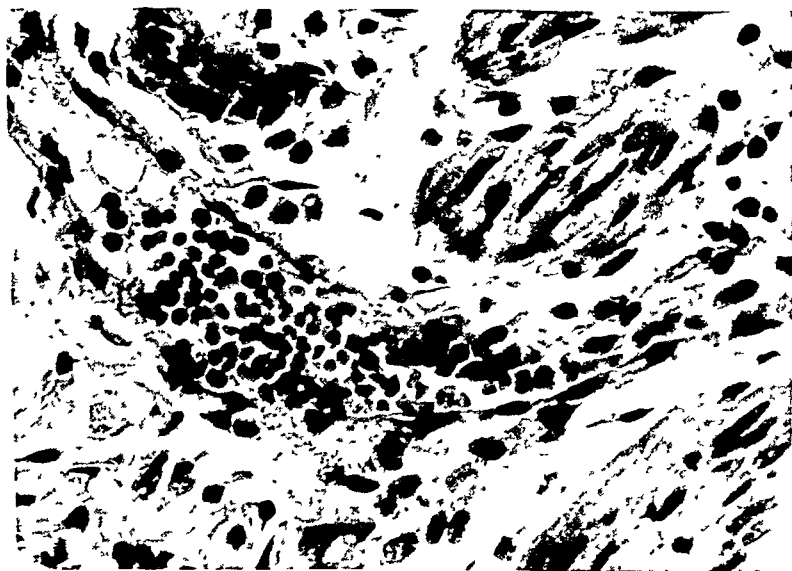


Fig. 2.—Wall of strawberry gall bladder. Many polymorphonuclear leucocytes are present in the capillaries in the muscular layer (hematoxylin and eosin $\times 435$).

Among the gall bladders selected for having an interval of twenty days or more between roentgenographic visualization with iodized dye

and operation, six had many polymorphonuclear leucocytes, twelve had a few, and seven had only occasional polymorphonuclear leucocytes (Fig. 4).

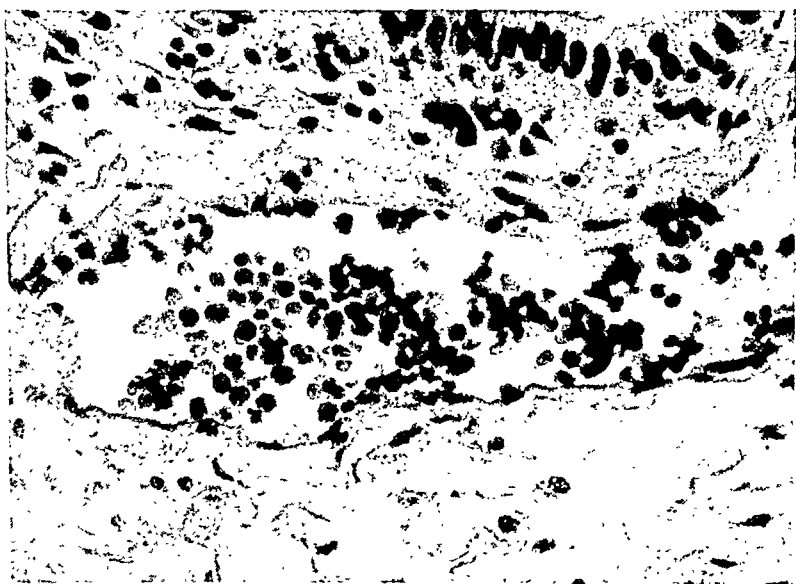


Fig. 3.—Wall of calcareous gall bladder. Many polymorphonuclear leucocytes can be seen in the capillary. Diapedesis is evident (hematoxylin and eosin $\times 435$).

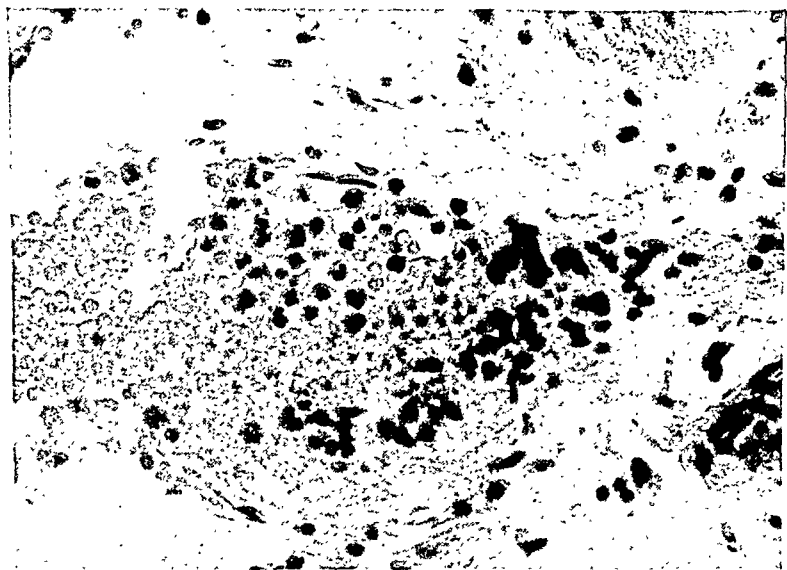


Fig. 4.—Wall of gall bladder. This patient had not been given dye recently. Many polymorphonuclear leucocytes can be seen in the capillary (hematoxylin and eosin $\times 435$).

In two of the ten normal gall bladders removed from dogs there were many polymorphonuclear leucocytes, in five there were a few, and in three there were occasional polymorphonuclear leucocytes (Fig. 5).

No polymorphonuclear leucocytes were seen in any of the sections of the fetal gall bladders.

The ten noninflamed appendices did not show a microscopic picture similar to that of the gall bladders. The polymorphonuclear leucocytes so consistently found in the capillaries of the gall bladder wall, often in greater numbers than the associated erythrocytes, were absent from the capillaries of the wall of the appendix. When larger vessels were sectioned, they showed polymorphonuclear leucocytes to be present only in a normal ratio to the erythrocytes present. There were usually numerous eosinophiles among the many lymphocytes.

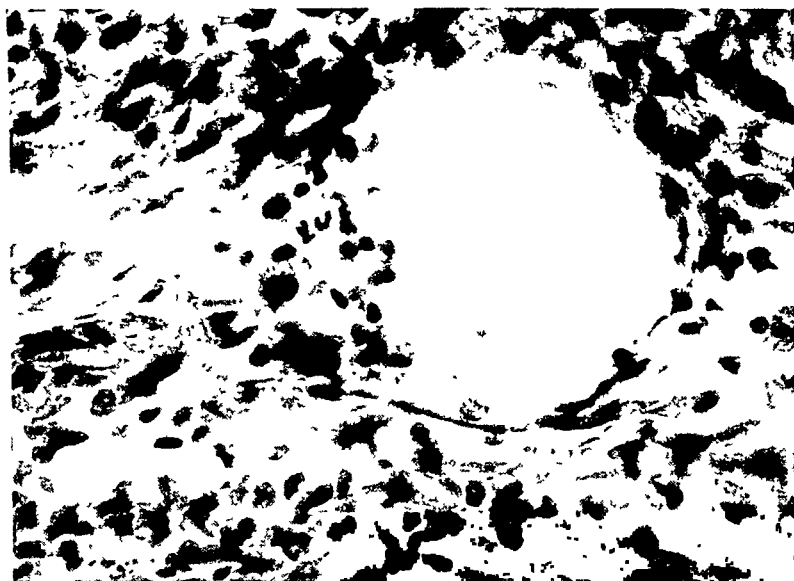


Fig. 5.—Wall of thin-walled noncalcareous gall bladder from a dog. Note the intra-luminal polymorphonuclear leucocytes (hematoxylin and eosin $\times 435$).

In the sections made of the jejunal specimens of human and canine origin, a picture of numerous intracapillary polymorphonuclear leucocytes in greater than normally expected numbers was seen. This was not always the case but consistently enough to be comparable to the sections of gall bladder in microscopic appearance.

COMMENT

The outstanding finding was not only the consistent presence of polymorphonuclear leucocytes in the thin-walled noncalcareous gall bladders but their presence in similar numbers in all the gall bladders examined except the nonfunctioning fetal gall bladders. These findings are not remarkable when compared with Mentzer's 612 necropsy cases in which he found evidence of microscopic inflammation in the form of polymorphonuclear leucocytes and lymphocytic cells in 75 per cent of the cases, in 7.7 per cent of which the patients died of gall bladder disease.

Eighty-two per cent of the surgically removed gall bladders in our study showed either many or few polymorphonuclear leucocytes in the wall. This excludes those gall bladders which contained only occasional polymorphonuclear leucocytes (Table I). Ordinarily all these gall bladders would be considered as showing evidences of inflammation. This figure is comparable to that of Mentzer.

As has been previously mentioned, none of these gall bladders had the gross appearance of acute inflammation and it does not seem too difficult to ascribe the presence of the polymorphonuclear leucocytes to a metabolic function rather than an inflammatory process, especially when the same microscopic picture could be seen in the gall bladders of dogs (Fig. 5). (Seventy per cent of the gall bladders removed from dogs, when examined microscopically, showed many or a few polymorphonuclear leucocytes.) In addition, if it is accepted that these polymorphonuclear leucocytes are serving a metabolic function, their complete absence from the nonfunctioning fetal gall bladders gives added weight to this interpretation.

Their absence in the noninflammatory appendix and their consistent presence in the human and canine jejunums, the former an organ of low absorptive function in comparison with the latter, which is of absorptive function, would also seem to indicate a metabolic function. Mackey⁷ referred to this seemingly analogous function of the intestinal epithelium and the known active resorption carried out by the gall bladder. Why could not a similar microscopic picture be indicative of a similar physiologic function?

Of all the gall bladders examined, the strawberry gall bladders appeared to contain the greatest number of polymorphonuclear leucocytes in their walls (Fig. 2). This is significant in that the increased number of polymorphonuclear leucocytes in such cases could represent an attempt to carry out a more rapid physiologic process, which is occurring to a lesser extent in all the other functioning gall bladders examined.

Finally, is there any proof to support this interpretation of metabolic function of these polymorphonuclear leucocytes in the gall bladder? Boyd,⁸ in his investigations of the pathology of the gall bladder, found that the endothelium of blood vessels in the gall bladder wall contained streaks of material which stained red with scarlet red. He also found this material in tissue inflammatory cells but did not mention polymorphonuclear leucocytes. Therefore, a series of surgically removed gall bladders were studied microscopically. The fresh frozen-section technique was used and the sections were stained with scarlet red for lipid. This was done without fixation of tissue to avoid losing fat or lipid. These sections showed the polymorphonuclear leucocytes to contain pale-staining granules, which when examined under the polarizing microscope were not doubly refractile. This would indicate that the granules were not cholesterol or cholesterol esters, but it seemed suf-

ficient proof that the polymorphonuclear leucocytes were carrying some type of lipoid and this was what was sought. This was not identification of the lipoid but proof of a function, metabolic in type to account for the presence of the polymorphonuclear leucocytes in the gall bladder for a purpose other than inflammatory.

Although Mackey⁷ did not mention the presence of polymorphonuclear leucocytes, he noted the presence of lipoid in the walls of gall bladders and stored in the stromal macrophages. He expressed the belief that this is a normal process, analogous to the process of resorption carried out by the intestinal epithelium and similar to resorption of other substances known to be carried out by the lining of the gall bladder.

CONCLUSIONS

1. The presence of polymorphonuclear leucocytes in the walls of the gall bladder, when examined microscopically, is not in itself an indication of inflammation when not associated with other signs of inflammation and should not be interpreted as such.

2. These polymorphonuclear leucocytes are serving a metabolic function rather than an inflammatory function when not associated with other signs of inflammation.

3. The iodized dye used in the preoperative roentgenographic visualization of the gall bladder does not have any association with the presence of the polymorphonuclear leucocytes in surgically removed specimens.

REFERENCES

1. Noble, J. F.: Relation of Hepatitis to Cholecystitis, *Am. J. Path.* 9: 473-496, 1933.
2. Boyd, William: *Surgical Pathology*, Ed. 5, Philadelphia, 1942, W. B. Saunders Company, p. 317.
3. Smith, L. W., and Gault, E. S.: *Essentials of Pathology*, Ed. 1, New York, 1938, D. Appleton-Century Company, Inc., p. 580.
4. McCartney, J. S.: Diseases of the Liver and Gall Bladder, in Bell, E. T.: *A Textbook of Pathology*, Ed. 5, Philadelphia, 1944, Lea & Febiger, p. 552.
5. Mentzer, S. H.: A Clinical and Pathologic Study of Cholecystitis and Cholelithiasis, *Surg., Gynec. & Obst.* 42: 782-793, 1926.
6. Maximow, A. A., and Bloom, William: *Textbook of Histology*, Ed. 3, Philadelphia, 1939, W. B. Saunders Company, p. 423.
7. Mackey, W. A.: Cholesterosis of the Gall-bladder: A Further Contribution to the Histology of This Condition, *Brit. J. Surg.* 28: 462-467, 1941.
8. Boyd, William: Studies in Gall-bladder Pathology, *Brit. J. Surg.* 10: 337-356, 1923.

GASTRIC SCHWANNOMA

REPORT OF A LARGE INTRAGASTRIC LESION SIMULATING A BEZOAR

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NONEPITHELIAL benign tumors of the stomach are very rare; even rarer are neurogenic tumors. However, Mines and Geschickter believe that approximately 10.9 per cent of benign tumors of the stomach are neurofibromas.

Ransom and Kay described, in 1940, seven lemmomas of which three were associated with other gastric disturbances and were discovered by accident.

The type of tumor here described is known in the medical literature by many names following the different microscopic aspects which it may present and the different descriptive opinions explaining its nature. Thus, Penfield considering it of connective tissue origin calls it perineural fibroblastoma; Verocay associates it with the nervous tissue and designates it neurinoma; the type due to Schwann's cells is called schwannoma (Masson) and lemmoma (Haeckel); Roussy, Lhermitte, and Cornill considering Schwann's cells as neuroglie cells (peripheric neuroglia) termed these tumors peripheric gliomas.

As it is not the object of this presentation to discuss the histogenesis and exact histologic picture of schwannomas, we suggest that those interested in this phase of the subject consult the brilliant works by Del Rio Ortega, Penfield, and Masson.

Our case is interesting because of the size of the tumor, because of its projection within the gastric cavity as a pedunculated neoplasia, and because of the several diagnostic possibilities to be considered.

The clinical report with all details is given in Case 1.

CASE REPORT

CASE 1.—The patient, J. G. M., 58-year-old Negro woman, was referred from the department of digestive diseases of the Municipal Hospital, Gral. Freyre de Andrade, to our surgical service. For one year she had had a discomfort in the left hypochondrium which extended to the epigastrium and felt like a ball. This was associated with indigestion, that is pyrosis, nausea, and a constant feeling of distention. She was constipated and suffered with flatulence. However, appetite was good. There was no pain. The epigastric mass changed position, and when it was on the right side the patient became very uncomfortable but was relieved by displacing it, especially when she had eaten. She rarely vomited but had lost much weight.

She looked rather old, the tongue was coated, and there was marked oral sepsis. The intensity of the heart tones and rhythms were normal. Over the apex there was a systolic murmur. The lungs were normal. On palpation of the abdomen

Read at a meeting of the National Surgery Society, May 26, 1944.

Received for publication, Aug. 8, 1944.

there was found in the left hypochondrium and under the costal border a hard, smooth, movable tumor, which could be displaced if pressure was made on it. Because of these characteristics and its position, this tumor could be easily confused with the spleen, although it was not typical of a spleen. The size of the liver was normal and the rest of the abdomen negative. There was lack of adipose and the skin was wrinkled and dehydrated. The blood pressure was 140/95; pulse was 72. The preoperative laboratory examinations were all normal.



Fig. 1.—Anteroposterior view with barium meal. The stomach never appeared filled with barium. The only free transit was through the lesser curvature.

The gastrokymogram showed an increase in the motor function and a decrease in the secretory function with hypochlorhydria at the beginning and anachlorhydria at the end. Occult blood was positive (++). The pylorus apparently opened with duodenal biliary reflux.

The roentgenogram demonstrated a foreign body occupying the whole gastric cavity, resembling a bezoar by the fluoroscopic and radiographic study (Figs. 1 and 2).

From this history it could not be determined that the patient had been in the habit of chewing hair or eating food rich in resin; she had never eaten caimito, sapote (Cuban fruit), or persimmons, or has never lived out in the country.

In spite of the fact that there was nothing in her history to suggest a gastric bezoar, we accepted the opinion of the radiologist, Dr. Padron, and operated upon the patient in search of the intragastric foreign body. The patient was previously prepared by hydration and repeated gastric lavage. The operation was performed Nov. 10, 1943. A midline supra-umbilical incision was made under spinal anesthesia (pantocain 0.018 gr.).

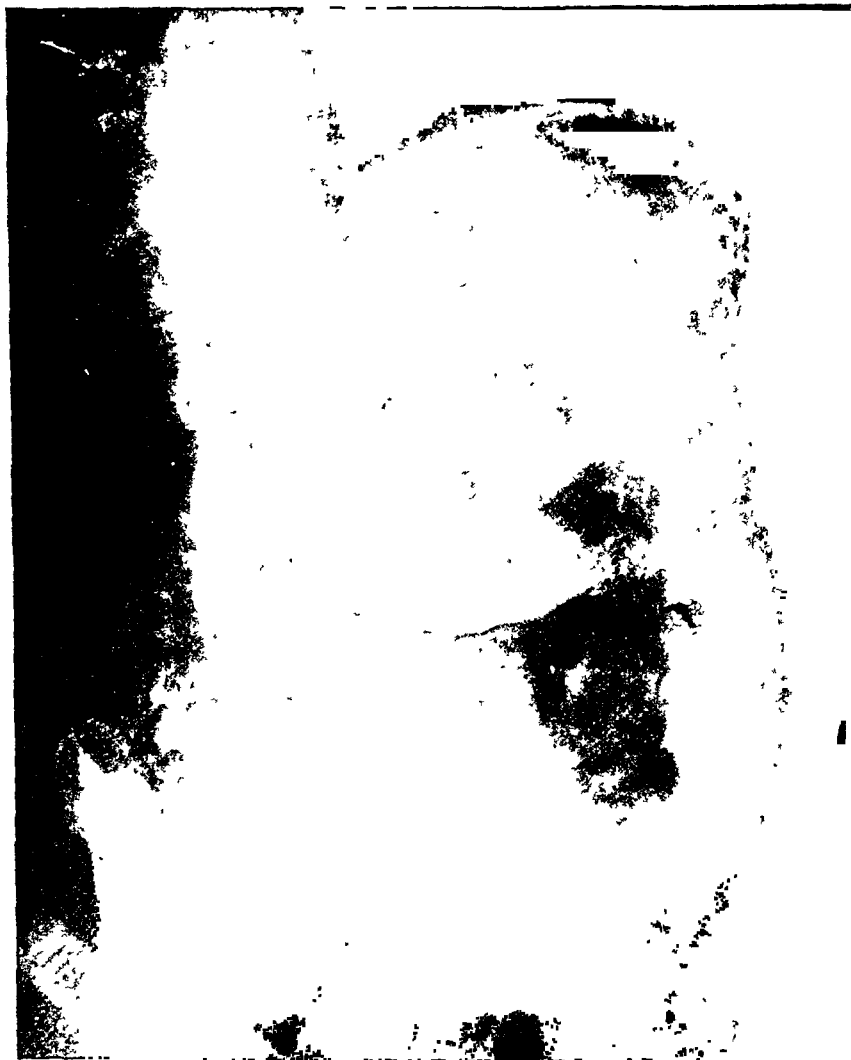


Fig. 2—Lateral view of the stomach with barium meal.

On opening the abdominal cavity it was demonstrated by palpation that the lesion was a pedunculated intragastric tumor. A longitudinal incision was made in the anterior wall of the stomach, after carefully walling off the peritoneal cavity (Fig. 3). After opening the stomach a large tumor occupying the entire gastric cavity was visualized. It was solid, dark red, and was attached by a pedicle to the

posterior wall of the fundus, from which it extended into the gastric cavity (Fig. 3). The tumor had assumed the shape of the stomach. By exerting traction on the tumor it was possible to exteriorize the pedunculated attachment of the tumor to the posterior wall of the fundus. The gastric mucosa covering the tumor in its entirety appeared thick because of an associated gastritis. With the the scalpel the mucosa was incised around the perimeter of the pedicle. The tumor was then easily removed. Careful hemostasis was secured, following which the mucosa of the

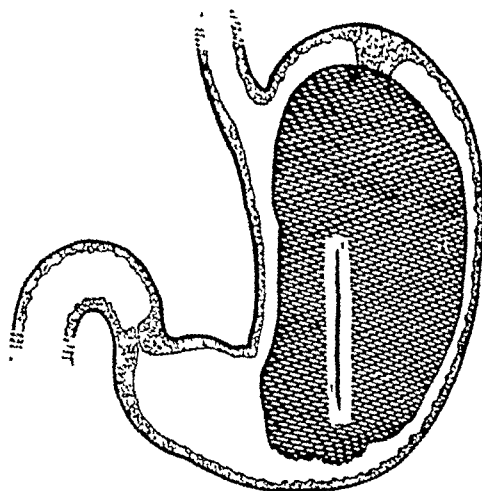


Fig 3—Schematic drawing to show the incision, shape, and situation of the tumor.

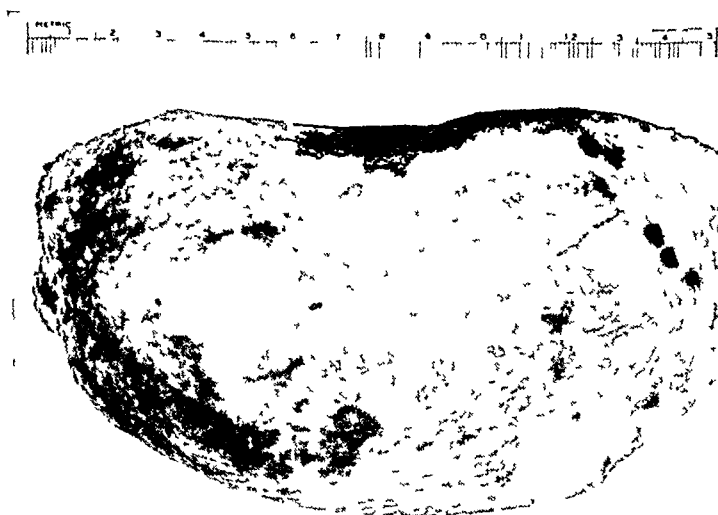


Fig 4—The tumor covered totally by gastric mucosa. Signs of chronic gastritis are seen in the lower pole.

superior and posterior walls of the stomach was sutured by means of a fine continuous intestinal catgut suture. The posterior wall was placed to its normal position, and it was observed that the suture of the mucosa remained in a high position and extended from right to left. The posterior wall of the stomach had not been opened or included in the suture, as evidenced by the fact that the serosa on the posterior surface was intact. Before the gastric wound was closed,



Fig. 5.—The tumor opened in the middle longitudinally. Notice the multiple pseudo-cystic cavities.



Fig. 6.—Microphotograph of the capsule of the tumor and the superficial layer of it. Notice a small nerve branch in the capsule (magnification $\times 80$).

incision of the gastric cavity was irrigated with hot saline solution which was aspirated. The gastrotomy opening was closed by a complete catgut suture and a seroserosal suture of linen, strengthened with several Cushing sutures. The suture line was dusted with sulfanilamide crystals, and the stomach replaced in its anatomic position. A Levin duodenal catheter was introduced for gastric decompression. Dextrose and saline solution and vitamin C were administered intravenously, and no food was allowed by mouth.

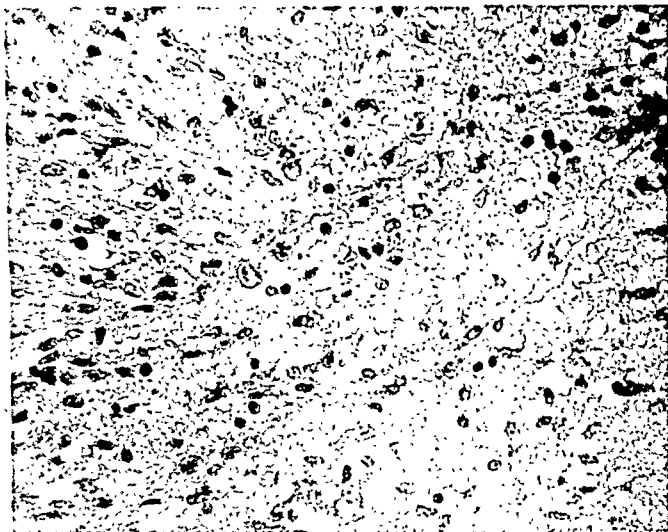


Fig. 7.—Microphotograph demonstrating myxomatous degeneration (magnification $\times 400$).

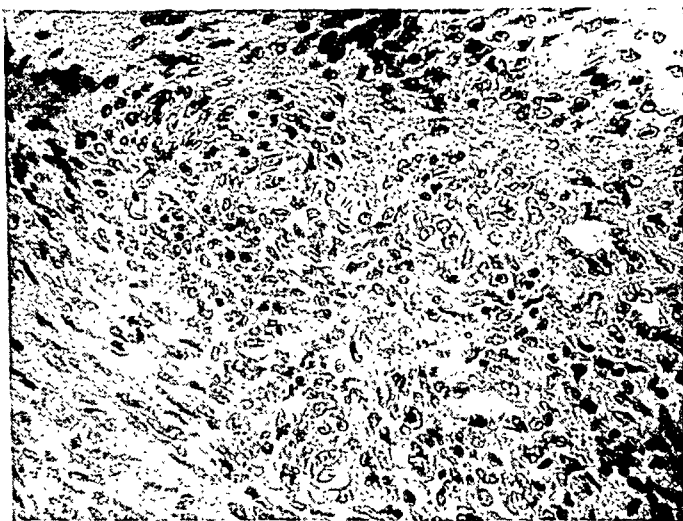


Fig. 8.—Microphotograph of the tumor showing a marked polymorphism of the cells. Nuclei and cells are scattered in different planes.

Pathologic Findings.—Macroscopic characters were: size 17 by 9 by 5 cm.; weight: 580 Gm. The tumor occupied most of the gastric cavity, and was movable, except where it was attached to the posterior wall by a pedicle one inch in diameter. The pedicle was centrally formed by connective tissue through which the tumor's

vessels ran. On the outside the rest of the pedicle was only gastric mucosa. With the exception of the pedicle the tumor was completely covered with gastric mucosa, and was separated from the mucosa by a thin connective tissue membrane (Fig. 4). On cutting, the consistence of the tumor felt soft; the surface appeared white yellowish with hemorrhagic points (Fig. 5).

Histologic Diagnosis.—The histologic diagnosis by one of us (F.L.B.) was schwannoma.

Postoperative Course.—The postoperative treatment (Figs. 6, 7, and 8) which was routine for these cases, consisted of the administration of small amounts of albuminous water, with periodic aspirations through the Levin catheter for several days.

The postoperative condition of the patient was normal but on the tenth day when the patient was ready to be discharged from the hospital after the wound was well healed and the sutures removed she had such a severe hematemesis that it appeared she might succumb, but with the quick assistance of an intern the acute anemia was quickly overcome. She was given a citrated blood transfusion, gastric lavages with hot physiologic saline solution, large doses of vitamin K, and an indwelling duodenal catheter was introduced. The gastric hemorrhage quickly stopped and the patient was discharged from the hospital nineteen days after the operation.

We have seen the patient recently; she is well and has gained twenty pounds in weight.

COMMENTS

The radiologic picture of this benign tumor of the stomach could easily be confused with any intragastric foreign body.

The clinical symptoms of these two conditions are not sufficient for an accurate diagnosis, which is quite difficult without radiologic examination. Benign tumors of the stomach are rare and only in the large ones can the diagnosis be suspected. A reason for making a mistake in the diagnosis in the case described was the unusual and peculiar location of this tumor. Most benign tumors are found at the greater curvature, at the fundus, or at the pyloric end of the stomach. Of all benign tumors, the one most easily diagnosed is the gastric polypus, because of its gastric symptoms and because they degenerate and ulcerate.

When benign gastric tumors are located near the pylorus they produce early symptoms of stenosis, which suggest to the physician the need for a radiologic investigation. On the other hand, if the benign tumors are small and away from the pylorus, they may present fewer or no gastric symptoms. Regarding gastric evacuation, we know that large-sized pedunculated tumors produce certain inertia of the muscles, and therefore produce a slow gastric evacuation; on the contrary, small-sized tumors excite the muscles and the evacuation is rapid. In the first group the stomach is hypotonic, whereas in the second it is hypertonic.

When, on examination of this patient, a tumor was found in the region of the stomach, even though there were few digestive symptoms, gastric x-ray was obtained. An intragastric lesion occupying the entire cavity was found. Logically, the first diagnosis was a gastric bezoar.

A gastric neoplasm seemed unlikely because of the few gastric symptoms and the history of its having been present for a year. On the other hand, the clinical picture in gastric bezoars develops insidiously and there are few, if any, symptoms and therefore gastric bezoars seemed likely.

Bezoars, as we all know, are concretions, like stones, which are found in the stomach of certain animals fed with food rich in resin. In ancient times these concretions were removed from the stomach of goats, camels, and cows, and sold as a medicament and the antidote of certain poisons. That is exactly what the Persian word *bezoar* means, literally translated, "protecting against poison."

Bezoars occur in those people who eat a great deal of caimito, sapote, raisins, etc., or vegetables rich in resins or fiber. Coming in contact with the hydrochloric acid of the stomach they are precipitated forming such large and hard nucleus that they cannot pass through the pylorus and must be removed operatively.

Bezoars formed by vegetable elements are called phytobezoars and those found in psychopathic persons in the habit of chewing and swallowing hair are called trichobezoars; a mixture of both being trichophytobezoars.

These foreign bodies and benign tumors of the stomach have similar clinical pictures and both require surgery. When the benign tumor is pedunculated and away from the pylorus, a relatively simple operation is all that is necessary, as in our case.

If the tumor is near the pylorus, producing stenosis, or if there is the slightest possibility of cancer, a partial gastrectomy is recommended as a rule.

When the tumor does not extend into the gastric cavity an elliptical incision is made through the gastric wall around the tumor, removing it in toto. The opening of the stomach is then closed in layers. Gastric polyposis, which does not disappear after medical treatment, requires total gastrectomy in some cases, because a polypus must be considered as a premalignant lesion.

An interesting feature of the case was the hypertrophic inflammatory reaction of the gastric mucosa covering the tumor. Also interesting was the fact that as the tumor was growing it assumed the shape of the gastric cavity and in spite of its size and weight the pedicle could hold it perfectly and the tumor was not resting on the gastric fundus. Undoubtedly if this had happened, the symptoms would have been more serious, and the patient would have sought treatment sooner.

The postoperative hemorrhage in this patient, ten days after the operation, risked her life. There are two explanations for this complication. In the first place there may have occurred a dehiscence of the gastric mucosa suture at the site of the tumor. Although the suture was high in the fundus of the stomach, it is possible that digestive

action of the hydrochloric acid dissolved the catgut and started the bleeding in spite of the perfectly made hemostasis at the time of the operation. On the other hand, an avitaminosis because of insufficient diet before, and even more so after, operation may have been a responsible factor in causing the massive gastric hemorrhage.

In the treatment of hematemesis following gastric surgery, we use blood transfusion, recommending it as an extraordinary and efficient hemostatic and antishock measure.

Gastric lavages with Levin catheter with lukewarm serum have given us good results, added to an adequate vitamin therapy. We want to make clear that the most important fact is the early attention given to a patient as soon as the first symptom of hemorrhage appears and that is why Levin's catheter used permanently is a safe treatment because by periodic aspiration and gastric lavage it is possible to stop any bleeding early.

SUMMARY

1. A case of a large-sized benign tumor of the neurogenic type (schwannoma) is reported.
2. Because of its radiologic features and few symptoms, it was confused with an intragastric bezoar.
3. The gastric neoplasm was removed transgastrically through an anterior gastrotomy. In spite of careful hemostasis and an otherwise normal convalescence, a massive gastric hemorrhage occurred on the tenth postoperative day. Convalescence otherwise was normal.

REFERENCES

1. Bockus, Henry L.: *Gastro-Enterology*, Vol. I, Philadelphia, 1943, W. B. Saunders Company, page 764.
2. Christopher, Frederick: *Textbook of Surgery*, Philadelphia, 1942, W. B. Saunders Company, page 1114.
3. Maingot, Rodney: *Abdominal Operations*, Vol. I, New York, 1940, D. Appleton-Century Co., Inc., page 486.
4. Masson, P.: Experimental and Spontaneous Schwannomas, *Am. J. Path.* 9: 367-388, 389-416, 1932.
5. Mines, J. F., and Geschickter, G. F.: Benign Tumors of Stomach, *Am. J. Cancer* 28: 136-149, 1936.
6. Penfield, W.: The Encapsulated Tumors of the Nervous System; Meningeal Fibroblastomata, Perineural Fibroblastomata and Neurofibromata of von Recklinghausen, *Surg., Gynec. & Obst.* 45: 178-188, 1927.
7. Ransom, H. K., and Kay, E. B.: Abdominal Neoplasms of Neurogenic Origin, *Ann. Surg.* 112: 700-746, 1940.
8. Rio Ortega, P. del: *Anatomía Microscópica de los Tumores del Sistema Nervioso Central y Periférico*, Madrid, 1934, pages 149-220.

PERFORATION OF THE RECTOSIGMOID

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WE ARE reporting from our service at the Metropolitan Hospital three cases of traumatic perforation of the rectosigmoid, one produced by rectal biopsy, one by the administration of a high colonic irrigation, and the third by the administration of an enema. All patients were operated upon, and two recovered, but one died.

CASE REPORTS

CASE 1.—W. W., a man, 67 years old, was admitted Jan. 20, 1941, with a chief complaint of rectal bleeding. Present illness had started eight months previously when the patient first noticed constipation and blood when straining at stool. Bleeding was not profuse nor was it painful. Within this period, there was a weight loss of twenty-seven pounds.

In general, the past history was essentially negative. Laboratory data were within normal limits. Rectal examination revealed the presence of external hemorrhoids and internal prolapsed hemorrhoids. In view of the history of constipation coinciding with the beginning of the rectal bleeding and weight loss, the possibility of a malignancy of the rectosigmoid or descending colon was entertained, and a sigmoidoscopy was recommended. This was done in the operating room preceding the removal of the hemorrhoids.

Under caudal anesthesia, a sigmoidoscope was passed gently to the 20 cm. mark. Examination revealed a polypoid mass about 15 cm. from the anal opening. Attempts to grasp this mass through the sigmoidoscope were unsuccessful, and the sigmoidoscope was removed. A finger was then inserted into the rectum and by applying pressure, the polypoid mass was reached, the finger hooked around it, and the mass drawn into the anal canal where it was grasped with an Allis forceps, and a section of the mass was excised for biopsy. The hemorrhoids were then excised in the routine manner (clamp and suture method).

During the afternoon of the operative day, the patient complained of lower abdominal pain. There was slight distention but no rigidity. The next day, there was marked tenderness. An X-ray taken on this day showed free air beneath the diaphragm, with moderate distention of the bowel and several fluid levels in the distended loops. Diagnosis was made of pelvic peritonitis secondary to traumatic perforation of the bowel. The patient was prepared for operation. The abdomen was entered through a left lower rectus incision. The small bowel and upper sigmoid appeared clean and not inflamed. The pelvic colon was exposed, and a longitudinal perforation $\frac{3}{4}$ inches in length was located anteriorly on the rectosigmoid just above the pelvic floor. This was closed with two rows of sutures. A rectal tube was passed through the anus and guided to a point 5 inches above the perforation. Fifty cubic centimeters of 5 per cent neoprotosil (at that time the sulphonamide preparation employed for peritoneal implantation) were instilled into the area, and the abdomen was then closed. Postoperatively, a Miller-Abbott tube

was passed and connected to a Wangensteen suction apparatus to maintain deflation of the bowel. In addition, sulfathiazole was given. The patient received blood transfusions and parenteral fluids.

Subsequently, the patient's temperature ranged between 100 and 103°F. On the fourth postoperative day, he had two bowel movements. Examination of the wound at this time showed marked purulent discharge and a partial dehiscence of the upper two-thirds of the abdominal wound. The wound was packed and strapped with flamed adhesive strips. The packing was removed on the sixth postoperative day, and new packing and adhesive strips were applied. The Miller-Abbott tube and the Wangensteen suction were working adequately, and the abdomen was not distended. By the ninth postoperative day, the temperature was normal, and the Miller-Abbott tube was removed. The wound appeared clean and was granulating. The packing was removed, but the adhesive strips were re-applied. The wound healed slowly but steadily, and the patient was discharged on the fifty-fourth postoperative day. Two months after discharge, the patient had no complaints, and the scar was well healed and solid.

The pathologic report of the biopsy of the rectum was hyperplastic glandular rectal mucosa, with no evidence of specific disease.

CASE 2.—M. B., a man, aged 63 years, was admitted March 6, 1944, with a chief complaint of severe abdominal pain. This patient was being treated at another hospital for hypertensive cardiovascular disease, generalized arteriosclerosis, osteoarthritis of hands, old cerebral thrombosis and right hemiparesis, and bilateral inguinal hernia.

Late in January, he was found to have hematuria, and cystoscopy and intravenous urography were performed but were essentially negative. March 6, 1944, the patient was being prepared for a repetition of the cystoscopy. A colonic irrigation was given as part of the preparation. During the time this irrigation was given, and, subsequently, he complained of severe abdominal pain. Later on, he began to vomit coffee ground material, and examination revealed a boardlike rigidity of the abdomen. A tentative diagnosis of perforated peptic ulcer was made, and the patient was transferred to the Metropolitan Hospital.

When first seen, this patient appeared acutely ill. He was markedly emaciated and in acute agony. He was lying on his left side with his knees drawn up and his trunk sharply flexed. Abdominal examination revealed generalized boardlike rigidity, tenderness, and rebound tenderness throughout the abdomen. Bilateral inguinal hernias were reducible and not particularly tender. Rectal examination showed tenderness in both iliac fossae. No masses were palpable. Diagnosis considered was spreading peritonitis due to perforated viscus, resulting from the high colonic irrigation; perforated peptic ulcer.

The patient was prepared for immediate surgery. Under local anesthesia, the abdomen was opened through a right rectus incision. About 200 c.c. of cloudy fluid were present, and this was aspirated and culture was taken. Examination of the sigmoid showed a perforation at the antimesenteric border about 6 inches from the rectosigmoid junction. This perforation was about 1¼ by 1½ cm. in size. The perforation was closed by three layers of sutures. No perforation was evident in the pyloric area. The abdomen was then closed without drainage.

Postoperatively, the patient received plasma and intravenous sodium sulfathiazole. A Levin tube was passed and connected to a suction apparatus. The patient's condition became progressively worse, and he died the day following the operation.

CASE 3.—J. V., a man, aged 55 years, was admitted Feb. 19, 1939, with a chief complaint of severe colicky abdominal pain. The patient had given himself an enema in the morning of the day of admission and immediately afterward experi-

enced the pain. The enema had been given because of constipation of one week's duration. The pain was made worse by body or abdominal movements. Vomiting occurred subsequently.

Previous to admission, he was being treated for carcinoma of the hard palate.

Eyes, ears, and nose were essentially negative. There was an ulcerated area on the hard palate; remainder of the mouth and throat were negative. There were several hard, small lymph glands in the left side of the neck. The heart and lungs were essentially normal. There was a boardlike rigidity of the abdominal muscles with tenderness and rebound tenderness throughout the abdomen. Liver dullness was not decreased. There was no distention. Rectal examination revealed only a moderately enlarged prostate.

The laboratory work-up was negative except for a trace of albumin in the urine and an increase in the polymorphonuclear leucocytes with a shift to the left. X-ray showed free air in the peritoneal cavity. The patient was operated upon about eleven hours after the enema was given, under a diagnosis of perforation of the sigmoid.

The abdomen was entered through a subumbilical left paramedian incision. A large amount of soapy, cloudy fluid was suctioned from the abdomen. The sigmoid was isolated, and a longitudinal perforation about 1 cm. long was found. This perforation was closed with two rows of sutures. Two drains were inserted into the abdomen; one into the cul-de-sac, and one to the left lateral wall. The abdomen was then closed in layers around the drains.

Postoperatively, the patient had a moderate temperature elevation for three days. On the fourth day, the temperature rose to 104°F., and there was moderate distention of the abdomen. This subsided by the fifth day, and from then on the temperature was only slightly elevated or normal. The abdominal wound became infected but healed slowly and steadily and was almost entirely closed at the time of discharge to the clinic for follow-up care on March 27, 1939.

DISCUSSION

In presenting these cases, it is our purpose to call attention again to the inherent dangers of perforation from mechanical manipulation in the relatively insensitive rectum and rectosigmoid even from the trauma of an enema. The avoidance of similar mishaps or at least an appreciable reduction in their incidence requires constant thought to the danger of perforation.

There is no instance in the American literature of a report by a man who is himself responsible for the accident,¹⁰⁻¹⁴ although numerous reports of accidental perforation have been made.^{8, 10, 14, 22, 23, 30, 32} Crohn and Rosenak¹⁰ have collected twenty-one cases of perforations by the sigmoidoscope by questionnaires directed to twenty-seven recognized proctologists and gastroenterologists in the United States. Of these perforations, five were produced by specialists, seven by assistants, five were seen in consultation after perforation had occurred, and no data are available concerning the remaining four cases.

Foreign literature abounds with reports of rectal injuries due to enemas and sigmoidoscopy (Ballon and Goldbloom,³ Pinnock,²² Gailbraith,¹² Rayer²⁴ and many others) while in this country, Goldman,¹³ Smiley,²⁷ Brumbaugh,⁸ and others have reported similar cases.

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have reduced the volume of infection when the contaminated fluid entered the peritoneum. At any rate, in this case, there was no generalized peritonitis found at operation eleven hours after the perforation had occurred, and the postoperative course was remarkably free of any clinical evidence of postoperative peritonitis.

When perforation, whatever its cause, has occurred, we are faced with an impending catastrophe unless we move with speed and accuracy. Crohn and Rosenak¹⁰ report a mortality of 47 per cent if operation is done within seven hours, and a mortality of 100 per cent if done from seven to seventy-two hours after perforation. Delayed diagnosis and, therefore, delayed operation results in generalized septic peritonitis with its inevitable high mortality.

While perforation is more likely to occur in cases presenting weakening of the intestinal wall by malignancy, diverticulum, ulceration, or colitis, many cases have been reported without essential pathology of the bowel. With such common use of high colonic irrigation, it is surprising that the incidence of perforation is not higher. Attention is again called to the indiscriminate use of the sigmoidoscope. Proper training in its use with constant attention to the details of its use, knowledge of anatomy of the area, sufficient lubrication, gentle handling without force or undue pushing, always with removal of the obturator after the instrument has entered the anal canal, with proper lighting to visualize the direction of the intestinal canal are safeguards for the prevention of accidents. Of utmost importance is a complete history as to previous operations or pelvic disease that might have given rise to obstructive bands or adhesions involving the rectosigmoid, preventing passage of the sigmoidoscope. Important also is a thorough preliminary examination of the patient who may present large pelvic tumors that preclude the use of the sigmoidoscope by their encroachment on the rectosigmoid. Particular care should also be used when the history reveals passage of blood by stool because this may indicate a weakened intestinal wall from tumor, colitis, diverticulitis, etc.

SUMMARY

Three cases have been presented of traumatic perforation of the rectosigmoid; one the result of intrarectal biopsy following sigmoidoscopy, one produced by a colonic irrigation, and the third by an enema. In all cases, the intestinal wall was normal and the perforation was purely traumatic. Sigmoidoscopy, even in highly trained hands, is not without danger. Other mechanical manipulations in this region are fraught with danger. Even a simple colonic irrigation or enema may result in perforation of the rectosigmoid or bowel. The fact that simple enema or colonic irrigation itself may result in perforation is to be considered in differential diagnosis of the acute abdomen.

REFERENCES

1. Andrew, E. W.: Pneumatic Rupture of the Intestine; A New Type of Industrial Accidents, Surg., Gynec. & Obst. 12: 63, 1911.
2. Bacon, H. E., and Reuther, T. F.: Wounds of the Anorectum and Their Treatment, S. Clin. North America 17: 1809, 1937.
3. Ballou, H. C., and Goldbloom, A.: Serious Injury to the Rectum From Improperly Administered Enemas, Canad. M. A. J. 45: 345, 1941.
4. Bastianelli, P.: La formula terapeutica chirurgica nel trattamento delle ferite del Retto, Policlinico (sez. chir.) 27: 241, 1920.
5. Behrend, M., and Herman, S. C.: Traumatic Perforation of Sigmoid Colon, J.A.M.A. 101: 1226, 1933.
6. Bendixen, P. A., and Blything, J. D.: Pneumatic Rupture of the Bowel, Surg., Gynec. & Obst. 18: 73, 1914.
7. Block, F. B., and Weissman: Pneumatic Rupture of the Sigmoid, J.A.M.A. 86: 1597, 1926.
8. Brumbaugh, C. G.: Rupture of the Rectum Resulting From Instrumentation, Atlantic M. J. 27: 651, 1924.
9. Burt, V. Con Amore: Pneumatic Rupture of the Intestinal Canal, Arch. Surg. 22: 875, 1931.
10. Crohn, B. B., and Rosenak, D. B.: Traumas Resulting From Sigmoid Manipulation, Am. J. Digest. Dis. 2: 678, 1936.
11. Dodds, D. I., and Mayeur, M. H.: Misguided Efforts at Abortion, Brit. M. J. 1: 1921, 1939.
12. Gailbraith, W. W.: Severe Rectal Injuries Caused by an Enema Given Through a Rigid Nozzle, Brit. M. J. 1: 859, 1937.
13. Goldman, C.: Rupture of the Rectum During Proctoscopic Examination, J.A.M.A. 93: 31, 1929.
14. Habbegger, C. J.: Impaling Injuries of the Pelvis, Wisconsin M. J. 10: 449-463, 500-520, 1912.
15. Kleehner, S. M.: Impalement of Rectum, Am. J. Digest. Dis. 1: 604, 1934.
16. Kortright, P. W.: Spontaneous Rupture of the Rectum, M. Times, New York 64: 296, 1936.
17. Kraker, A. D.: Foreign Body in the Rectum and Sigmoid, Am. J. Surg. 29: 449, 1935.
18. Manheim, S.: Personal Communication.
19. Pearse, E. H.: Instrumental Perforation of the Rectosigmoid, Arch. Surg. 42: 850, 1941.
20. Peek, L. A.: Gunshot Wounds of the Rectum, J. Florida M. A. 14: 396, 1928.
21. Pennington, J. R.: Rectum; Anus and Pelvic Colon, Philadelphia, The Blackiston Company.
22. Pinnock, D. D.: Dangerous Rectal Trauma Due to Rigid Nozzle, Lancet 1: 205, 1937.
23. Powers, H. J., and O'Meara, S. E.: Perforated Wound of the Rectum Into the Pouch of Douglas Caused by Impalement, Ann. Surg. 109: 468, 1939.
24. Rayer, H. H.: Injury to the Rectum Caused by Faulty Administration of Enema, Brit. M. J. 1: 419, 1932.
25. Sallick, A. M.: The Conservative Management of the Sigmoidoscopic Perforation, SURGERY 8: 473, 1940.
26. Scott, W. W.: Repair of the Rectal Tear and Rectourethral Fistula, J. Urol. 33: 643, 1935.
27. Smiley, E. K.: Instrumental Perforation of the Rectum, California & West. Med. 39: 329, 1933.
28. Suermondt, W. F.: Spontaneous Rupture of the Rectum, Year Book of Surgery, 503, 1935.
29. Walking, A.: Rupture of the Sigmoid by Hydrostatic Pressure, Ann. Surg. 102: 471, 1935.
30. Wollenweber: Sodomy With Dog Resulting in Rectal Wounds and Death From Peritonitis, Deutsche Ztschr. f. d. ges. gerichtl. Med. 34: 457, 1941.

REGIONAL ENTERITIS OF THE PROXIMAL JEJUNUM FOLLOWING TRAUMA

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THE clinicopathologic syndrome of terminal ileitis was brought to the attention of the medical profession in 1932.¹ Since then our concepts of the disease have changed greatly, as evidenced by the changes in terminology, namely: regional enteritis, regional enterocolitis, regional cicatrizing enteritis, granulomatous jejuno-ileitis. These changes in terminology bespeak the variations in opinion about the anatomic location of this lesion.

The most common site involved is still the terminal ileum (Table I). Of 200 cases reported by Crohn and Yunch,² only seventeen were diffuse or involved higher portions of the ileojejunum. Of their forty-three cases, Warren and Miller³ found twenty-seven with involvement of the terminal ileum, ten with involvement of the cecum, and two with involvement of other areas of the small bowel. Sussman and Wachtel⁴ state that 60 per cent of their twenty-three cases affected the terminal ileum, and although they referred to the occurrence of localized jejunitis, none is reported in their series. Bockus,⁵ in a series of twenty-one cases, found none involving the jejunum. Brown and Donald,⁶ reporting on the experiences at the Mayo Clinic, found only 5 of 178 cases of enteritis primarily involving the jejunum. While Browne and McHardy,⁷ in a comprehensive review of over 1,000,000 hospital admissions and 7,970 autopsies, found only one case of enteritis involving the jejunum. Ravdin and Johnston,⁸ in a review of the literature in 1939, tabulated 462 cases of regional enteritis, of which only sixteen involved the jejunum. Harris and co-workers⁹ were among the first to report a case of cicatrizing enteritis wholly confined to the jejunum. The first constriction in this case began, however, about 60 cm. below the ligament of Treitz. Several single cases involving the jejunum are found in the more recent literature.¹⁰⁻¹² In none of these is the lesion confined to the most proximal portion of the jejunum. In Johnson's case,¹¹ the first stenotic area was about three inches below the ligament of Treitz, and skip areas involved about forty inches of small bowel. In Brewster's¹² case, the first area of constriction was about two and one-half feet below the ligament of Treitz.

The case reported here is of interest, not only because of the confinement of the pathology to the most proximal portion of the jejunum, but also because of the preceding trauma which may have an etiologic relationship in the pathogenesis of the lesion.

Received for publication, Oct. 27, 1944.

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TABLE I
FREQUENCY OF INVOLVEMENT OF JEJUNUM IN REPORTED CASES OF
REGIONAL ENTERITIS

AUTHOR	TOTAL NUMBER OF CASES	NUMBER INVOLVING ILEOJEJUNUM	JEJUNUM
Crohn and Yunich	200	17	
Warren and Miller	43	2	
Bockus	21	0	0
Ravdin and Johnston	462		16
Brown and Donald	178		5

CASE REPORT

A 23-year-old soldier was hospitalized July 3, 1943, for injuries sustained that day when the motorcycle which he was driving ran into the rear end of a truck, the motorcycle driving on under the body of the truck. The exact manner in which the injuries were sustained could not be determined because the patient was asleep at the time of the collision and was unconscious for a short time afterwards. He sustained multiple lacerations and abrasions of the face, mainly the forehead and left cheek, and a depressed, compound fracture of the left maxilla and zygoma, as well as a fracture of the fifth rib. His principal complaint was severe, generalized abdominal pain which apparently was not cramplike.

On examination the abdomen did not appear distended and there was no visible sign of abdominal wall contusion. There was generalized abdominal tenderness, but this seemed more somatic than visceral. Peristalsis was audible. Flat plate of the abdomen was taken and no free air in the peritoneal cavity was seen.

The abdominal pain subsided within nine days. During this period the patient continued to pass flatus and have bowel movements, but vomited only a few times. The facial fracture required extensive surgical interference. There were no symptoms referable to the abdomen until the end of August, or about seven weeks after the accident, when for three days he became constipated and suffered malaise and abdominal discomfort; all of these symptoms were for the most part relieved by an enema and a saline cathartic. However, there remained some residual and abdominal soreness. In spite of some apprehension about the condition of his abdomen since the accident, the patient ate well throughout the attack, did not vomit, and eventually resumed normal bowel habits.

Physical examination at this time revealed mild abdominal tenderness with slight accentuation in the left upper quadrant but, with continued tenderness over the fractured left rib. This was thought to be of little significance. His symptoms having subsided, he was given a furlough for thirty days.

Upon his return from furlough, the patient stated that he had become much worse. Vomiting occurred after nearly every meal. This was accompanied by abdominal pain which was said to be generalized. Only light and liquid foods were taken but the vomiting continued. In spite of this, his bowel habits remained normal.

Physical findings still remained equivocal, with abdominal tenderness diffuse and no distention being present. The temperature remained normal. There was no leucocytosis. The sedimentation rate was 6 mm. per hour. Stool cultures were negative for pathogenic microorganisms.

Roentgenographic examination of the gastrointestinal tract, following a barium sulfate meal, showed the stomach and duodenum to be dilated, the duodenum to a marked degree. The opaque medium was almost completely arrested at the level of the ligament of Treitz. Distal to this part for about twelve inches, the jejunum

showed a complete loss of mucosal markings, marked stenosis, and absence of peristaltic waves. During fluoroscopic examination it was noted that this portion of the bowel was rigid and nondistensible (Figs. 1 and 2). While there was a scattering of barium in the rest of the small bowel, no further organic constriction was demonstrated. Study of the involved portion of the bowel with the Miller-Abbott tube yielded no additional information.

With this evidence, a diagnosis of stenosing obstructive lesion of the proximal jejunum was made and the patient prepared for operation by continuous Wangensteen suction and parenteral fluids. The symptoms of obstruction became prominent before the operation, but no mass could be palpated abdominally, and no visible peristalsis was detected.



Fig. 1.

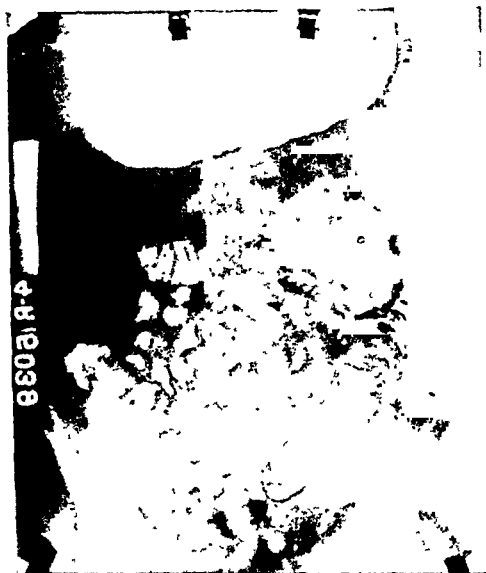


Fig. 2.

Fig. 1.—Roentgenogram of stomach, duodenum, and proximal jejunum one hour after administration of a barium sulfate meal, showing gastric and duodenal dilatation as well as the stiffness, loss of mucosal markings, and constrictions of jejunum.

Fig. 2.—Four hours after the administration of barium sulfate, showing that very little of the meal has left the stomach. The involved portion of jejunum is well outlined.

Oct. 14, 1943, an exploratory laparotomy was performed under general anesthesia. The findings were surprising. The most proximal twelve inches of the jejunum, beginning at the ligament of Treitz, were bright in color, appeared indurated and edematous, and could be likened to a piece of garden hose in consistency. The mesentery, too, was markedly edematous and contained numerous enlarged glands. In fact, glands were palpable and visible throughout the entire mesentery of the small intestine, decreasing in size caudally. The appearance of the involved bowel and mesentery was not unlike that of a subacute, nonspecific, regional enteritis. It was obvious that this was the cause of the obstruction. The stomach itself was dilated, but otherwise appeared normal. Because of the acuteness of the process, and because of its extension into the duodenum, it was decided not to remove the bowel at this time but rather to do a short circuiting operation and put the involved portion of the bowel at rest. Accordingly, a posterior gastrojejunostomy was effected, leaving a loop of jejunum of approximately twenty-two inches. One of the regional mesenteric glands was removed for biopsy.

The biopsied lymph node showed a marked increase of plasma cells and some polymorphonuclear leucocytes. The endothelial cells appeared swollen. The pathologist called this a subacute lymphadenitis, and stated that the findings were not inconsistent with a diagnosis of regional enteritis.

Postoperative convalescence was without incident and the patient was up and about the ward within two weeks, tolerating a diet low in roughage but high in calories and vitamins. He was free of obstructive symptoms. However, it was necessary to maintain him on a low residue diet, as roughage seemed to produce some abdominal discomfort and occasional vomiting. The patient was observed for about five months, during the latter portion of which time he complained of inability to eat a large meal and stated that for one or two hours after nearly every meal he had some cramplike pains in the epigastrium, following which period the pains subsided and he was again comfortable. It began to affect his food intake, for because of the pain he purposely omitted meals. However, his general condition was not affected and although his former weight was not regained, he maintained his current weight. After a barium sulfate meal, x-ray examination of the upper gastrointestinal tract was done and it was noted that while the gastroenterostomy stoma was functioning well, some barium passed through the pylorus into the duodenum where it was literally churned, and then regurgitated into the stomach from where it entered into the jejunum through the enterostomy. The duodenum was markedly dilated and the deformity and obstructive lesions in the jejunum were still evident.

The patient was again operated upon,* March 26, 1944, under spinal anesthesia. The acuteness of the inflammatory process had subsided. The proximal portion of the jejunum was no longer red or indurated but appeared shriveled and constricted in areas, and the color was a dull and lustreless pink. The regional glands were still enlarged but the general appearance was that of a chronic process. The duodenum was markedly dilated but otherwise normal. The mesenteric lymphadenitis noted generally at the previous operation had subsided everywhere except in the immediate area attached to the involved jejunum. The gastroenterostomy was taken down and the first twelve inches of the jejunum resected, utilizing an end-to-end anastomosis of the remaining segments.

The postoperative course was again without incident and the patient was again up and about the ward within two weeks. Following a suitable time in which foods were introduced gradually, an unqualified full diet was prescribed and taken without difficulty, the patient was sent on a thirty-day furlough from which he returned about fifteen pounds heavier and in excellent general health and spirits. At that time he had no complaints.

Gastrointestinal roentgenogram two months after the last operation showed that the duodenum had returned to almost normal size and the motility was normal. Gastroscopic examination revealed the remains of a scar at the site of the old gastroenterostomy.

The specimen removed consisted of the first 40 cm. of jejunum (Fig. 3). The proximal 3 cm. were dilated but showed an absence of the plicae circulares. Following this there was a constricted area followed by another dilated area in which the plicae circulares were absent. In all there were three areas of constriction, and in about 12 cm. the plicae circulares were absent. Dilated blood vessels were seen in the serosa and the mesenteric lymph nodes were enlarged. Microscopically the stenotic areas showed a loss of normal architecture of the mucosal glands and in some areas there was a complete loss of the epithelial element, in which case they were replaced by neutrophils and round cells. The entire submucosa was markedly thickened and contained large aggregates of plasma cells, small round cells, and scattered

*This operation was performed by Dr. Alton Ochsner.

eosinophiles. An occasional giant cell was present in the submucosa. The muscle layers were distorted and the serosa was markedly thickened, edematous, and contained dilated blood vessels. In the areas where the villi were intact and no gross lesions of the mucosa were seen, infiltration of plasma and round cells about the glands was evident. The submucosa consisted of a dense, highly vascularized connective tissue. The pathologic diagnosis was regional enteritis.



Fig. 3.—Photograph of resected portion of jejunum and attached mesentery, showing dilations and constrictions and loss of plicae circulares.

DISCUSSION

Etiology.—Much has been written, but little is known, about the etiology of regional enteritis. Because of the microscopic features simulating a low-grade inflammatory process or granuloma, tuberculosis was thought of as a possible etiologic agent. Exhaustive investigation yielded no evidence that the tubercle bacillus is the cause of this type of enteritis,^{8, 13} although a true tuberculous enteritis may masquerade as a regional enteritis. Outstanding among other organisms incriminated are those of the *Shigella* group. Felsen¹⁴ has claimed an etiologic relationship between the *Shigella* organisms and regional enteritis, as well as ulcerative colitis, on the basis of epidemiologic, bacteriologic, and serologic studies. This viewpoint has not gained widespread acceptance and most workers in the field deny that a specific bacterial agent has been demonstrated to be the cause of this disease. Ravdin and Johnston,⁸ in their comprehensive review, refer to no less than twelve possible etiologic factors: (1) bacteria, (2) bacterial toxins, (3) viruses, (4) protozoa, (5) metazoa, (6) achylia gastrica, (7) allergy, (8) foreign bodies, (9) nonspecific inflammation of appendix, (10) impairment of blood supply, (11) interference with lymphatic supply, and (12) trauma.

Trauma is an etiologic factor about which varying opinions have been expressed. Crohn¹¹ denies that there is a cause and effect relationship between trauma and regional enteritis, and where the history of preceding trauma is obtained, the latter may be an unrelated coincidence, or at most an aggravating factor. Contrary to this is a report by Reichert and Mathes¹⁵ of a 40-year-old man who developed cramplike abdominal pain, associated with vomiting and diarrhea, two weeks after a severe blow to the abdomen from the steering wheel of an automobile. The symptoms gradually increased and two months later an operation was required. Upon exploration of the peritoneal cavity, a portion of the ileum which was apparently traumatized at the time of the accident was found kinked and bound down by adhesions. The mesentery was short, thick, and boggy, and contained dark-colored material at its roots. No glandular involvement was described. Because of enlargement of the lacteals, lymphatic obstruction was advanced as an important etiologic factor. In experimental animals, Reichert and Mathes¹⁵ succeeded in producing cicatrizing contractions of various parts of the bowels by injecting sclerosing agents into the subserosal and mesenteric lymphatics. Bell,¹⁶ however, was unable to produce cicatrizing enteritis or any lesion simulating the condition by interfering with the blood supply to the intestinal tract.

Traumatizing surgical procedures and intestinal trauma from intrinsic causes have been incriminated as possible causes of granulomatous intestinal lesions. Leonardo¹⁷ described a case of ileocecal granuloma developing only eleven days after a very difficult appendectomy, necessitating much traumatization. In 1928, before regional enteritis was established as a disease entity, Ginsburg and Klein¹⁸ reported three cases of stenotic lesions of the small bowel, developing two weeks to five months after the relief of strangulated inguinal hernia. The thought is expressed that interference with blood supply, insufficient to cause gangrene, may result in enough devitalization of tissue to produce cicatricial changes. Two types of lesions are described, an annular type and a tubular type. In another paper, Ginsburg and Oppenheimer¹⁹ point out that "nonspecific granulomas of the intestine" may form secondary to sealed perforation and secondary to known vascular disturbance of the gut. In a paper on "Ineffective Granuloma," Mock²⁰ discusses various factors that may encourage the formation of chronic granuloma of the intestines. He discusses surgical trauma at great length. He refers to granulomas developing about silk sutures and those forming around ligatures of omentum or mesentery as well as around foreign bodies left in the peritoneal cavity. In regard to extraneous injuries he says, "The importance of trauma in the forming of these obscure intra-abdominal tumor masses, so often mistaken for malignant tumors, has never been sufficiently stressed. No case of granuloma as the direct result of an accident, such as from an automobile or a fall, has ever been reported, I believe."

In our case the trauma is a challenging factor in the production of the final lesion. While a definite cause and effect relationship cannot be established, there are many features which favor such a possibility. The patient had no symptoms whatever before the accident, yet the disease progressed rapidly to a stenosis once the symptoms became manifest. The portion of the gut involved is one that would be more subject to external trauma because of its relatively fixed anatomic position. The limitation of the lesion to a small segment of terminal ileum is not uncommon. However, when the lesion involves more proximal portions of gut, skip areas occur with great regularity. In our case the pathologic process remained limited to the jejunum throughout the five months' interval between the two surgical procedures.

On the other hand, it is difficult to conceive how trauma by itself can produce a lesion that is essentially inflammatory in character. The usual type of traumatic injury of the hollow viscera is a perforation. Kelly,²¹ in discussing nonpenetrating abdominal injuries, found that intestinal perforation occurred in all of his cases of severe injury. Another method by which severe injury to the gut could be produced through trauma is from hemorrhage or other vascular damage. However, in this case, no evidence of extensive hemorrhage was seen at operation or could be presumed clinically. In the case reported by Reichert and Mathes,¹⁵ the finding of dark-colored material at the root of the mesentery was suggestive of old hemorrhage. The lapse of nearly two months between the injury and the development of symptoms is also surprising. Finally, in this mechanical age when abdominal trauma is common, it would be suspected that such cases as ours will be reported in the literature with greater frequency.

One case, however, that bears some resemblance to ours is that described by Pupini,²² in which a 36-year-old man sustained an injury to the abdomen by falling against the steering wheel of a launch. In this case symptoms occurred immediately and continued without remission until he was admitted to the hospital two months later. The symptoms were those of intestinal obstruction. Upon exploration, about 10 cm. of mid-ileum were found involved. Gross appearance of the bowel was similar to the appearance of the jejunum in our case at the first operation. No glandular involvement is mentioned and no microscopic description is given. In the case of regional jejunitis reported by Browne and McHardy,⁷ a history of severe abdominal trauma was elicited. Severe symptoms in their case occurred seven days after the abdominal trauma. The lesion involved the mid-portion of the jejunum which appeared thickened and "acutely inflamed." Microscopically, the bowel wall showed acute exudative and chronic inflammatory changes. There is no mention of enlarged mesenteric lymph nodes.

Symptomatically, the case reported presents the unusual but rational sequence that one would expect in inflammatory and stenosing lesions at the proximal end of the small intestine. There is less emphasis upon

disturbance of bowel function as represented by diarrhea and constipation, more upon upper abdominal distress and vomiting closely simulating the picture of pyloric obstruction.

Even though the inflammatory lesions subsided after the first operation, the patient continued to have mild symptoms, apparently because of the mechanical difficulties in the dilated loop of the duodenum. In spite of the functioning gastroenterostomy stoma, some material entered the blind loop of duodenum. The patient became practically asymptomatic after resection of the involved loop of the jejunum.

SUMMARY AND CONCLUSIONS

1. A case of regional enteritis confined to the proximal jejunum is presented.

2. The symptoms began about two months after a nonpenetrating injury to the abdomen.

3. The possible etiologic relationship of trauma to regional enteritis is discussed.

REFERENCE

1. Crohn, B. B., Ginsburg, L., and Oppenheimer, G. D.: Regional Ileitis, *J. A. M. A.* 99: 1323, 1932.
2. Crohn, B. B., and Yunich, A. M.: Ileo-Jejunitis, *Ann. Surg.* 113: 371, 1941.
3. Warren, R., and Miller, R. H.: Regional Enteritis: Forty-Three Cases, *New England J. Med.* 226: 589, 1942.
4. Sussman, M. L., and Wachtel, E.: Granulomatous Jejuno-ileitis, *Radiology* 39: 48, 1942.
5. Bockus, Henry L.: *Gastroenterology*, Vol. II, Philadelphia, 1943, W. B. Saunders Company, Page 158.
6. Brown, P. W., and Donald, C. J., Jr.: Regional Enteritis, Prognosis, *Am. J. Digest. Dis.* 9: 87, 1942.
7. Browne, D. C., and McHardy, G.: Primary Lesions of the Jejunum, *J. A. M. A.* 115: 2257, 1940.
8. Ravdin, J. S., and Johnston, C. G.: Regional Ileitis: A Summary of the Literature, *Am. J. M. Sc.* 198: 269, 1939.
9. Harris, F. J., Bell, G. H., and Brown, H.: Chronic Cicatrizing Enteritis, *Surg., Gynec. & Obst.* 57: 637, 1933.
10. Gage, C. H.: Crohn's Disease, *Brit. J. Radiol.* 15: 272, 1942.
11. Johnson, W. R.: Chronic, Nonspecific, Jejunitis With Unusual Features, *Gastroenterology* 1: 347, 1943.
12. Brewster, H. N., quoted by Crohn, B. B.: *Gastroenterology* 1: 353, 1943.
13. Crohn, B. B.: On Portis, Sidney, Chapter on Regional Ileitis, in *Diseases of Digestive System*, Philadelphia, 1941, Lea & Febiger.
14. Felsen, J.: New Clinical Concepts of Bacillary Dysentery: Its Relationship to Non-specific Ulcerative Colitis, Distal Ileitis and Non-specific Granuloma, *Am. J. Digest. Dis.* 3: 86, 1936; The Relationship of Bacillary Dysentery to Distal Ileitis, Chronic Ulcerative Colitis and Non-specific Intestinal Granuloma, *Ann. Int. Med.* 10: 645, 1936.
15. Reichert, F. L., and Mathes, M. E.: Experimental Lymphedema of the Intestinal Tract and Its Relation to Regional Cicatrizing Enteritis, *Am. J. Surg.* 104: 601, 1936.
16. Bell, H. G.: Chronic Cicatrizing Enteritis, *California & West. Med.* 41: 239, 1934.
17. Leonardo, R. A.: Intestinal Obstruction Due to Non-specific Ileocecal Granuloma, *Am. J. Surg.* 35: 607, 1937.
18. Ginsburg, L., and Klein, E.: Late Intestinal Stenosis Following Strangulated Hernia, *Am. J. Surg.* 88: 204, 1928.
19. Ginsburg, L., and Oppenheimer, G. D.: Non-specific Granulomata of the Intestines, *Am. J. Surg.* 98: 1046, 1933.
20. Mock, Harry E.: Infective Granuloma, *Surg., Gynec. & Obst.* 52: 672, 1931.
21. Kelly, E. C.: Non-penetrating Abdominal Trauma, *Surgery* 14: 163, 1943.
22. Pupini, Guido: Study of a Case of Post-traumatic Intestinal Stenosis, *Polidinicco (sez. prat.)* 39: 847, 1932.

INTRAPERITONEAL ABSORPTION PATTERNS OF SULFONAMIDE DRUGS (WITH SPECIAL REFERENCE TO MICROCRYSTALLINE SULFATHIAZOLE) AND A COMPARISON OF COINCIDENT CONCENTRATIONS IN THE PORTAL VEIN, SYSTEMIC CIRCULATION, AND PERITONEAL FLUID

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THE purposes of this paper are: (1) to demonstrate the absorption curves of sulfonamide drugs, with special reference to microcrystalline sulfathiazole,* in the normal peritoneal cavity and (2) to compare the concentrations of these drugs in the portal and systemic veins and in the free peritoneal fluid.

Increasing attention has been given to the administration intraperitoneally of sulfonamide drugs of greater antibacterial potency than sulfanilamide.^{1, 2, 3, 6, 7, 9, 11, 17, 20, 21, 24} However, the lower solubilities and certain other differences in physical properties of such compounds, especially sulfathiazole and sulfadiazine, make the commonly used method of sprinkling the crystalline material into the peritoneal cavity even more objectionable than when sulfanilamide is so introduced. Microcrystalline sulfonamides² would appear to offer means of obtaining more complete dispersion of the sulfonamide in the abdomen and of avoiding, to some extent at least, the foreign body reaction caused by caking and clumping of the material when introduced by sprinkling. Furthermore, when employed in the finely divided state of microcrystals, solution of the sulfonamide occurs much more rapidly because of the much larger surfaces exposed to the solvent action of the body fluids so that higher concentrations are obtained. Favorable results have been reported by Ferguson⁷ and by Chambers, Harris, Schumann, and Ferguson² when microcrystalline sulfathiazole was employed locally for therapeutics in a variety of conditions. The latter have also described the response of rabbits and dogs to intraperitoneal administration of sulfathiazole in the form of microcrystals.

Experiments described in this paper were designed to provide additional information concerning the behavior of microcrystalline sulfathiazole introduced into the abdomen of the dog. The influence of the method of administration, whether as powder or suspension, also has

Received for publication, July 3, 1944.

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been investigated. The rate of absorption of sulfathiazole from the peritoneum was studied by means of serial determinations of its concentration in the peripheral blood. However, the possibility that this does not provide an adequate measurement must be considered, and statements to this effect have been made,⁵ a marked uptake of drug by the liver with resulting injurious effects having been postulated. One of us has pointed out¹⁵ that the evidence did not warrant the inferences based thereon. Examination of the portal blood was included in our studies to make certain that microcrystalline sulfathiazole might not differ in this respect from ordinary sulfathiazole. Peritoneal fluid also has been examined when present.

TECHNIQUE

Sulfonamide drugs, 0.28 Gm. per kilogram of body weight, were administered into the peritoneal cavities of normal dogs. Microcrystalline sulfathiazole suspension (20 per cent in gelatin) was given through an 18 gauge needle inserted through the abdominal wall; no anesthesia was necessary. Approximately two minutes were required to empty the syringe. In order to avoid complications caused by caking, which often occurs when sulfonamide drugs are dusted into the peritoneum, microcrystalline sulfathiazole powder, sulfathiazole powder, and sulfanilamide powder were insufflated with a Shelanski vaginal insufflator through a 1 cm. incision, using an open technique for incising the peritoneum developed by one of us for peritoneoscopy.¹⁶ Sodium pentothal anesthesia was used. At stated intervals, blood was taken by venipuncture. Plasma was used for sulfathiazole determinations, and whole blood for sulfanilamide. At approximately the time that maximum systemic sulfonamide levels were expected, the animals were anesthetized by intravenous nembutal, 0.33 to 0.44 Gm. per kilogram, and subjected to laparotomy. Peritoneal fluid was aspirated, after which blood was withdrawn from the portal vein and from the heart. Liver biopsy was then performed. The incisions were closed in layers. Additional venipunctures were performed postoperatively. Peritoneal fluid was filtered before it was analyzed.

RESULTS

Insufflation of sulfanilamide into the peritoneal cavity (Fig. 1) caused a rise in blood sulfanilamide, more rapid than that described by Jackson and Coller¹² following implantation of sulfanilamide in peritoneal cavities of dogs but similar in other respects. Lower values were obtained by Keeley.¹³ Ambrose and Haag¹ used only 0.1 Gm. per kilogram and their results thus cannot be compared directly with ours.

Insufflation of sulfathiazole in its ordinary crystalline form led to peak values two to three hours after administration of the drug, distinctly later than those obtained after sulfanilamide (Fig. 2). The

graphs obtained by plotting concentration in plasma against time resemble those shown for whole blood by Ambrose and Haag,¹ differences in height of the rise being explained in part by the higher dosage employed in our experiments, and in part by the difference between plasma

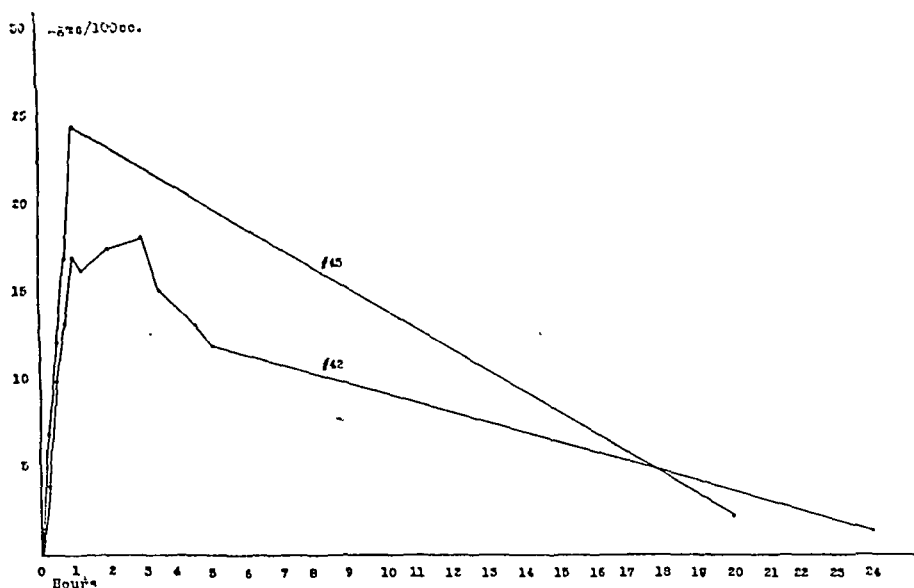


Fig. 1.—Blood sulfanilamide concentration after intraperitoneal insufflation of sulfanilamide.

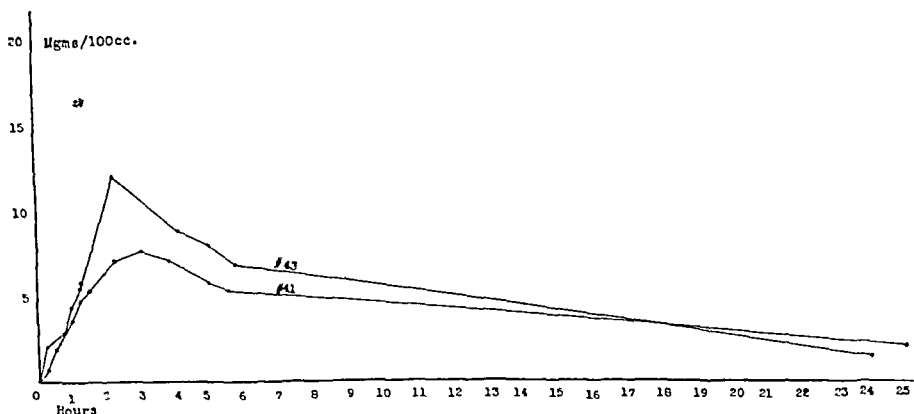


Fig. 2.—Plasma sulfathiazole concentration after intraperitoneal insufflation of sulfathiazole powder.

and whole blood sulfathiazole concentrations. (Plasma sulfathiazole concentrations are ordinarily about 25 to 35 per cent higher than corresponding concentrations in whole blood.)

Insufflation of microcrystalline sulfathiazole caused a rise to an average of about 12 mg. per 100 c.c. in plasma. No marked difference in plasma sulfathiazole concentrations is evident (Fig. 3) as compared with

the response to ordinary crystals of sulfathiazole. There is some indication that the curves for the latter may be lower, although it is impossible to draw conclusions from two experiments.

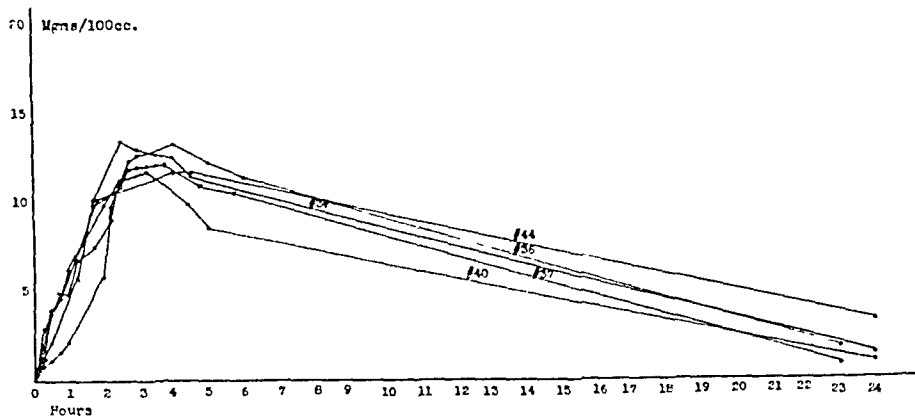


Fig. 3.—Plasma sulfathiazole concentration after intraperitoneal insufflation of microcrystalline sulfathiazole powder.

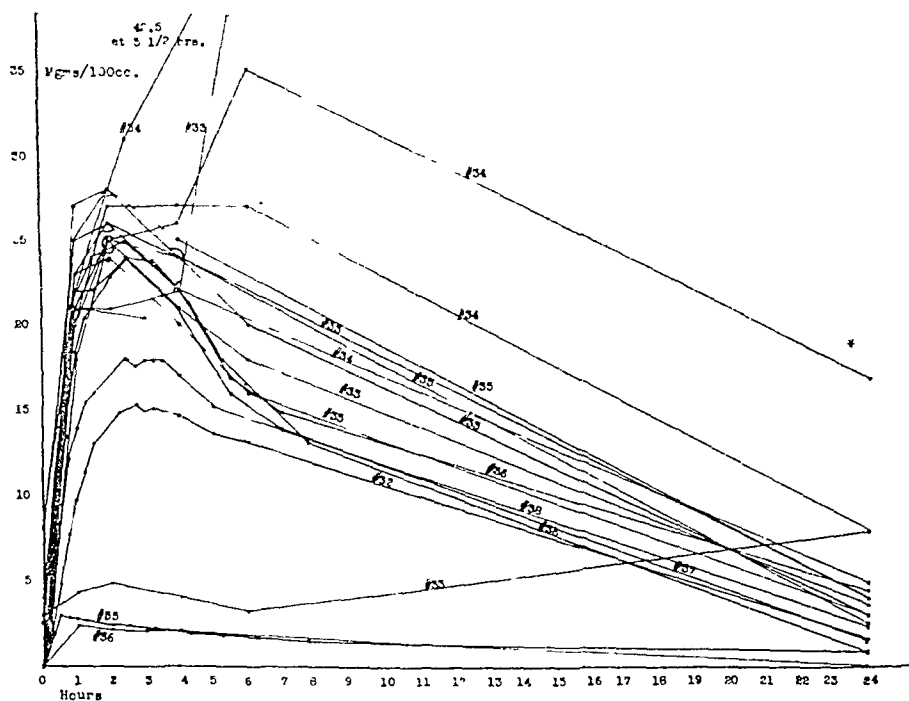


Fig. 4.—Plasma sulfathiazole concentration after intraperitoneal injection of microcrystalline sulfathiazole suspension.

Intraperitoneal injection of a suspension of microcrystalline sulfathiazole usually caused an immediate and striking rise in plasma sulfathiazole concentration to levels considerably higher than those ordinarily attained when other methods or routes of administration were used (Fig. 4). Thus, at one hour an average plasma sulfathiazole of 18.2

mg. per 100 c.c. was observed, at two hours this had risen to 20.7, at four hours it was 18.9, and at six hours it was 18.6 (Fig. 5). Our results confirm those of Chambers, Harris, Schumann, and Ferguson.² Gilchrist and his associates⁹ found even higher values but used larger doses.

The results of three experiments differed from the remaining seventeen in that only slight increases occurred in plasma drug concentration after intraperitoneal administrations of sulfathiazole microcrystal suspension. The technique employed in making the injections, it is believed, precluded the possibility of piercing a viscus, and the high level found twenty-four hours after the injection in Dog 33 eliminates

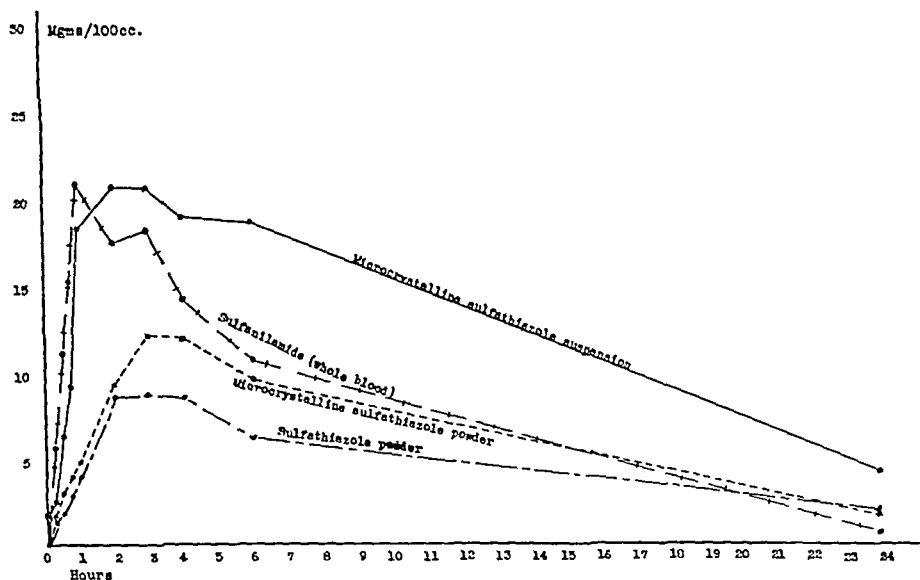


Fig. 5.—Mean plasma sulfonamide concentration after intraperitoneal implantation of sulfonamide drugs.

such an explanation. Furthermore, laparotomy done on Dog 32 in the course of another experiment in which the rise in drug concentration in plasma was less than 1 mg. per 100 c.c. showed the drug to be present in the peritoneal cavity in the form of globules 1 to 2 mm. in diameter. In this state a relatively small surface would be exposed to the solvent action of peritoneal fluid and absorption might be delayed.

In two experiments after an initial rise, followed by a period of several hours characterized by comparatively stable concentrations, a marked secondary rise in plasma sulfathiazole occurred. This again might be caused by increased dispersion of the suspension of microcrystals. Another possible explanation is an increase in solution of the sulfathiazole following stimulation of the formation of peritoneal fluid by the drug. Because of the low solubility of these substances, the volume of fluid available together with its protein content will be one of

the factors limiting the rate of absorption. Protein is important because of the existence of sulfathiazole-protein complex. Also to be considered is the existence of more than one pathway by which transfer from the peritoneal space to the blood stream could occur.

Sulfathiazole concentrations exceeding 35 mg. per 100 c.c. of plasma were observed in three experiments. In each, a similar experiment had been done on the preceding day and some residual sulfathiazole was found in the plasma at the start of the experiment. However, other experiments under similar conditions failed to show exceptionally high levels and in one dog little rise over the residual level occurred after administration of a second dose intraperitoneally.

Fig. 5 shows the mean concentration curves for sulfanilamide, sulfathiazole, microcrystalline sulfathiazole powder, and microcrystalline sulfathiazole suspension.

Table I shows concentrations of sulfonamide drugs in plasma or blood samples collected at the same time from the heart and from the portal vein. In some instances peritoneal fluid was collected and analyzed as well. The drug concentrations in portal and heart blood are the same. The results are in agreement with those of Jackson and Collier who found no differences in sulfanilamide concentrations between portal and peripheral blood four hours after intraperitoneal administration. Maximal differences were observed by them within thirty minutes after the

TABLE I
COMPARISON OF COINCIDENT SULFONAMIDE LEVELS IN THE PORTAL AND SYSTEMIC CIRCULATION AND IN THE PERITONEAL FLUID

DOG NO.	DRUG	PERITONEAL FLUID (MG. PER 100 C.C.)	TIME (MIN.)	PORTAL BLOOD (MG. PER 100 C.C.)	RATIO OF PORTAL BLOOD LEVEL OVER PERITONEAL FLUID LEVEL	TIME (MIN.)	HEART BLOOD (MG. PER 100 C.C.)	RATIO OF HEART BLOOD LEVEL OVER PORTAL BLOOD LEVEL
45	Sulfanilamide powder	106.0 (serosang.)	60	25.6	0.24	70	24.5	0.96
42	Sulfanilamide powder	38.0	180	18.2	0.48	175	18.2	1.00
43	Sulfathiazole powder	27.0 (serosang.)	240	10.0	0.41	253	8.9	0.89
41	Sulfathiazole powder	75.0 (serosang.)	180	8.4	0.11	175	7.7	0.92
44	Microcrystalline sulfathiazole powder	49.0 (serosang.)	240	11.9	0.24	240	11.8	0.99
40	Microcrystalline sulfathiazole powder	98.0	150	10.4	0.11	150	11.3	1.09
37	Microcrystalline sulfathiazole suspension	172.0	150	13.0	0.08	150	13.6	1.05
35	Microcrystalline sulfathiazole suspension	Not done	180	20.5	---	180	20.0	0.98
34	Microcrystalline sulfathiazole suspension	No free fluid	350	42.9	---	350	42.5	0.99
33	Microcrystalline sulfathiazole suspension	Not done	360	39.8	---	320	38.2	0.96
Mean				20.1	0.24		19.7	0.98±0.06

drug was implanted, when the portal blood concentration was 40 per cent higher than that of the peripheral blood, but the concentrations soon approximated those of the peripheral blood. Obviously, comparisons of drug concentrations in portal and peripheral circulation can be evaluated only when distribution through the body is complete and equilibrium between tissues and plasma has been attained.

As is to be expected, high concentrations of sulfathiazole or sulfanilamide drug are present in the peritoneal fluid. The number of specimens is insufficient to evaluate the concentrations in peritoneal fluid established by the several forms of sulfathiazole tested. The highest concentrations, however, are to be seen in the fluids taken after injection of the suspension of microcrystals.

The incidence of vomiting was high in those experiments in which the suspension of sulfathiazole microcrystals was used, occurring in nine of twenty-two experiments. Sulfathiazole administered in comparable dosages in other forms did not cause vomiting.

Small amounts of fluid were found in the peritoneal cavity in nine of eleven experiments. Of these, five showed clear fluid and four showed fluid that was slightly serosanguinous. The serosanguinous fluid in each instance was found in those experiments in which incisions had been made for insufflation.

DISCUSSION

The rate of absorption of sulfonamide compounds from the peritoneal cavity depends on many factors: the chemical nature of the compound used, its physical state, the method of administration, the extent of binding by protein, specific differences in permeability, and the state of the peritoneum. It appears that plasma levels, in turn, depend on the ease of absorption, the availability of the drug for excretion, and the extent of tubular reabsorption in the kidney. In this study of intraperitoneal administration it is shown that crystal size as well as the use of a suspension, as compared with insufflation, greatly influences the rate at which sulfathiazole enters the blood. Similar differences between sulfathiazole administered as a powder and as a suspension were observed by Crutcher, Daniel, and Billings.³

A noteworthy feature of the experiments dealing with intraperitoneal injection of a suspension of sulfathiazole microcrystals is the high concentrations of this drug that are established in the plasma. At a given dosage rate, sulfathiazole administered orally fails to reach levels as high as those characteristic of sulfanilamide, sulfapyridine, sulfadiazine, or sulfamerazine, mainly due to the fact that it is so readily excreted. Thus, the average concentration of 20 mg. per 100 c.c. maintained for several hours exceeds any that can be obtained by other means save continuous intravenous administration of the sodium salt. Multiple subcutaneous injections of saline suspensions of sulfathiazole by Poth and Fernandez¹⁷ gave comparable concentrations but only with much larger amounts of drug. The frequency with which vomiting occurred

at such high levels, however, suggests that somewhat smaller amounts be employed by this route. Despite the variable response to single injections, our experience with repeated intraperitoneal injections, although limited, points to this as a promising procedure enabling maintenance and a degree of control of blood sulfonamide levels.

It has already been pointed out by one of us (Pearce¹⁵) that apprehensions concerning excessively high concentrations of sulfanilamide in the portal blood following intraperitoneal administration were not warranted. Our experiments demonstrate that sulfathiazole, like sulfanilamide (Jackson and Collier¹²), showed no significant differences between drug concentrations in portal and systemic circulation within one hour after the drug was given. Differences such as those observed by Jackson and Collier¹² occurred only for a comparatively short time after the drug was administered. Rapid transfer of the drug from peripheral blood to tissues before the concentration in the latter reaches the point of equilibrium could explain these initial differences. Thus, it is unnecessary to postulate a selective absorption by the liver. We observed no physical evidences of hepatitis despite some high plasma sulfathiazole concentrations obtained with the microcrystalline suspension. Judgment must be reserved, however, until a detailed histologic study of liver biopsies has been completed.

Differences in rate and extent of absorption of these drugs are to be anticipated in the presence of the pathologic peritoneum. Inflammatory processes, where free peritoneal fluid is found and the peritoneal surfaces become edematous, tend to decrease absorption from the serous surfaces, although in the initial phase of peritonitis, when simple capillary hyperemia alone is present, absorption may be increased. When well-organized barriers such as abscesses are formed, peritoneal absorption may be slowed and high local drug concentrations may remain for long periods as shown by clinical observations of protracted blood levels. Rates of absorption shown in the present experiments, therefore, are more rapid than those encountered in disease involving the peritoneum.

High local concentrations of sulfonamides have a greater bacteriostatic effect than low concentrations of the drugs. According to Mueller and Thompson¹⁴ more organisms may be affected and the drug action becomes bactericidal. Evidence from many sources^{4, 8, 10, 12, 14, 18, 19, 22, 23} testifies to the value of sulfanilamide implanted in the peritoneal cavity. However, Epps, Ley, and Howard,⁶ Stafford,²¹ and Poth and Fernandez¹⁷ found sulfathiazole to be more effective in peritonitis than were other sulfonamide drugs. The latter found that a combination of high blood concentrations maintained together with high local concentrations is the best response. Whether sulfathiazole is the drug of choice for such a purpose requires additional study, since despite its high antibacterial activity the greater rapidity with which it is excreted and the possibility of complications in the urinary tract and other toxic manifestations may

make sulfadiazine or sulfamerazine preferable. Sulfadiazine is available in microcrystalline form and has been studied after being implanted into the peritoneal cavity at operation by Hawking and Hunt.¹¹ Absorption was incomplete and sulfadiazine lumps surrounded by adhesions and lymph were found at necropsy ten days postoperatively. Presumably, use of a suspension of microcrystals would obviate this complication. Sulfadiazine powder has been employed intraperitoneally with good results by Ryan, Bauman, and Mulholland²⁰ and Walter and Cole.²⁴ However, Crutcher, Daniel, and Billings³ found a more marked inflammatory reaction caused by sulfadiazine than by sulfanilamide or sulfathiazole. Differences in the chemical and physiologic behavior of the various sulfonamide drugs are sufficiently marked to make obligatory a detailed study of each when employed in a new dosage, form, or route of administration.

Because of the facility with which suspensions of microcrystalline sulfonamide can be injected directly into the peritoneal cavity, application of this form of therapy suggests itself in the treatment of peritonitis and the management of blast injuries. The use of penicillin intraperitoneally also awaits investigation.

SUMMARY

1. Sulfathiazole introduced into the peritoneal cavity of normal dogs in the form of microcrystals was more rapidly absorbed than was crystalline sulfathiazole when compared on the basis of concentrations of drug in the plasma.

2. Microcrystalline sulfathiazole injected into the peritoneum as a suspension gave higher concentrations of drug in blood plasma than did comparable amounts administered by insufflation, although the response to the former was not uniform.

3. High and sustained concentrations of sulfathiazole in plasma can be obtained by intraperitoneal injection of a suspension of microcrystals.

4. Simultaneously collected samples of blood from portal vein and heart contained practically identical concentrations of sulfonamide drugs 60 to 360 minutes after intraperitoneal administration either as crystals or microcrystals.

REFERENCES

1. Ambrose, A. M., and Haag, H. B.: *Comparative Blood Concentrations of Sulfaguanidine, Sulfanilamide, and Sulfathiazole After Administration Orally, Peritoneally, and Pleurally to Dogs*, *SURGERY* 12: 919, 1942.
2. Chambers, L. A., Harris, T. N., Schumann, F., and Ferguson, L. K.: *The Use of Microcrystals of Sulfathiazole in Surgery*, *J. A. M. A.* 119: 324, 1942.
3. Crutcher, R. R., Daniel, Jr., R. A., and Billings, F. T.: *The Effect of Sulfanilamide, Sulfathiazole, and Sulfadiazine Upon the Peritoneum*, *Ann. Surg.* 117: 677, 1943.
4. Dees, J. G.: *Valuable Adjunct in Perforated Appendices*, *Mississippi Doctor* 18: 215, 1940.
5. Editorial: *J. A. M. A.* 119: 796, 1942.

6. Epps, C. H., Ley, E. B., and Howard, R. M.: Treatment of Peritonitis: Intraperitoneal Use of Sulfonamides Based Upon Animal Experiments, Surg., Gynec. & Obst. 74: 176, 1942.
7. Ferguson, L. K.: Local Use of Sulfonamide Compounds, J. A. M. A. 118: 1514, 1942.
8. Garlock, J. H., and Seeley, G. P.: The Use of Sulfanilamide in Surgery of the Colon and Rectum, SURGERY 5: 787, 1939.
9. Gilchrist, R. K., Straus, F. H., Hanselman, R., Draa, C. C., Lawton, S. E., and Freeland, M.: Traumatic Peritonitis: Choice of Routes for Administration of Sulfonamides, Surg., Gynec. & Obst. 76: 689, 1943.
10. Graham, A. F.: Subcutaneous and Intraperitoneal Use of Sulfanilamide, S. Clin. North America 21: 577, 1941.
11. Hawking, F., and Hunt, A. H.: Absorption of Sulfonamides Used Locally, Brit. M. J. 2: 604, 1942.
12. Jackson, H. C., and Collier, F. A.: The Use of Sulfanilamide in the Peritoneum, J. A. M. A. 118: 194, 1942.
13. Keeley, J. L.: Intraperitoneal Administration of Sulfanilamide; Concentration in Peripheral Blood in Dogs, Proc. Soc. Exper. Biol. & Med. 46: 458, 1941.
14. Mueller, R. S., and Thompson, J. E.: The Local Use of Sulfanilamide in the Treatment of Peritoneal Infections, J. A. M. A. 118: 189, 1942.
15. Pearce, A. E.: Letter to Editor, J. A. M. A. 120: 982, 1942.
16. Pearce, A. E.: Open Peritoneoscopic Technic. Unpublished data.
17. Poth, E. J., and Fernandez, E. B.: Experimental Studies of the Value of Sulfathiazole, SURGERY 13: 847, 1943.
18. Rippy, E. L.: Perforating Gunshot Wounds of the Abdomen, J. A. M. A. 115: 1760, 1940.
19. Rosenburg, S., and Wall, N.: The Treatment of Diffuse Peritonitis by Direct Intraperitoneal Introduction of Sulfanilamide, Surg., Gynec. & Obst. 72: 722, 1941.
20. Ryan, J. D., Bauman, E., and Mulholland, J. H.: The Blood Concentration and Urinary Excretion of Sulfadiazine Following Intraperitoneal Administration, J. A. M. A. 119: 484, 1942.
21. Stafford, E. S.: Value of Sulfathiazole in Treatment of Peritonitis or Abscesses of Appendiceal Origin, Surg., Gynec. & Obst. 74: 368, 1942.
22. Tashiro, K., Pratt, O. B., Kobayashi, N., and Kawaichi, H. K.: The Local Implantation of Sulfanilamide in the Peritoneal Cavity and Its Clinical Application in Peritonitis, SURGERY 11: 671, 1942.
23. Thompson, J. E., Brabson, J. A., and Walker, J. M.: The Intraabdominal Application of Sulfanilamide in Acute Appendicitis, Surg., Gynec. & Obst. 72: 722, 1941.
24. Walter, L., and Cole, W. H.: The Intraperitoneal Administration of Sulfadiazine With Special Reference to a Comparative Study With Sulfanilamide, Surg., Gynec. & Obst. 76: 524, 1943.

AN IMPROVED METHOD FOR THE IMPLANTATION OF SULFONAMIDE COMPOUNDS IN THE ABDOMINAL CAVITY AND LOCAL WOUNDS

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WE ASSEMBLED, in 1943, an apparatus to implant sulfanilamide powder or crystals in the abdominal cavity, more satisfactorily and efficiently than merely to pour or dump the drug in the abdomen from a test tube or sterile envelope. This method also guards against the formation of lumps and small masses which may become insoluble masses and act as foreign bodies.

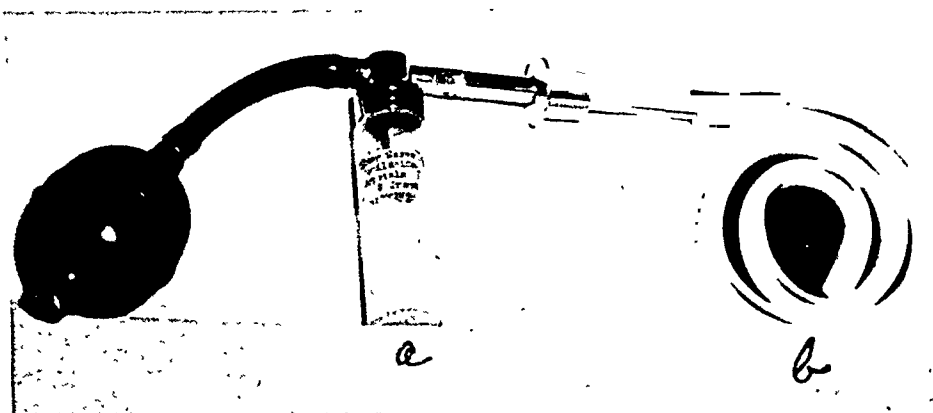


Fig. 1.—A, The insufflator; B, rubber tubing eighteen inches long.

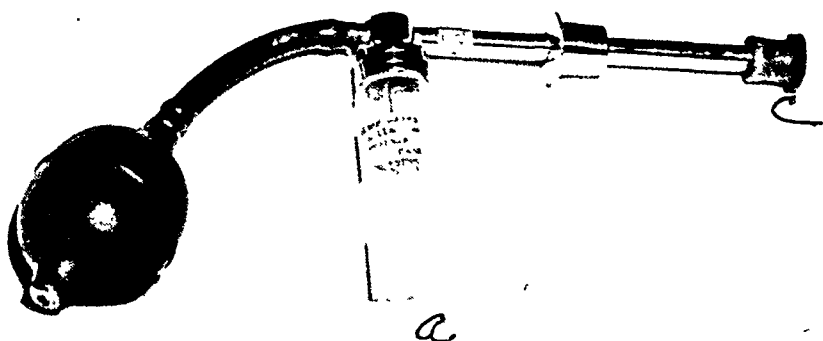


Fig. 2.—A, The insufflator; C, small piece of rubber tubing tied off at one end to protect the tip of the insufflator when not in use.

Figs. 1 and 2 show the parts of the apparatus.* The insufflator (A), rubber tubing eighteen inches long (B), and small piece of rubber tubing tied off at one end to protect the tip of the insufflator when not in use.

Received for publication, Nov. 10, 1944.

*This apparatus was made up at my suggestion but assembled by the operating room supervisor at the St. Joseph's Hospital.

It is our custom to load the sterile insufflator with 8 Gm. of sterile sulfanilamide crystals for each case in order to have an amount sufficient for implantation of the abdominal cavity to spray the drainage tract on the way out, as well as the abdominal wound itself. We use the sulfanilamide crystals, exclusively.

In the treatment of local wounds the insufflator without the attached rubber tubing is very satisfactory and permits implanting the wound thoroughly, regardless of location or position and without the danger of lump formation of the drug.

The care of the apparatus is as follows: The insufflator is wrapped in double covers and autoclaved under nineteen pounds pressure at 250° F. for thirty minutes. The rubber tubing is washed in soap and water, rinsed once in tap water and three times in distilled water, coiled up, wrapped in double covers, and autoclaved under fifteen pounds pressure at 250° F. for fifteen minutes.

COMMENTS

This simple apparatus is handy and very satisfactory, a decided improvement over any other method of which I have any knowledge. The operator has the advantage of being able to implant the drug in the form of a spray, anywhere in the abdominal cavity, without handling or traumatizing the abdominal contents.

THE VALUE OF STAPHYLOCOCCUS TOXOID IN THE TREATMENT AND PREVENTION OF CHRONIC STAPHYLOCOCCUS INFECTIONS

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INTRODUCTION

THE treatment and prevention of chronic staphylococcus infections, particularly of recurrent furunculosis and axillary abscesses, has always been one of the major problems confronting general practitioners and surgeons. It is known that the use of vaccines, various chemicals, such as "stenoxyl" and sulfanilamide derivatives, x-ray and ultraviolet irradiation, autochemotherapy, and many other methods of treatment have not fulfilled their expectations. It is natural, therefore, that the discovery of staphylococcus toxin¹⁻⁵ and its ability to produce antitoxin⁶⁻¹¹ attracted wide attention as a possible method of treatment and prevention of staphylococcus infections.

LITERATURE

The discovery of Burnet¹² that staphylococcus toxin could be detoxified by formaldehyde without the loss of its antigenic power, greatly simplified the matter of immunization. This led to the wide clinical use of a detoxified toxin known in different countries as toxoid or anatoxin.

Significant Factors in the Preparation of Toxoid in the Literature.—

1. *General laboratory observations:* At the present time we know of four different staphylococcus toxins, namely hemolysin, leucocidin, necrotoxin, and lethal toxin, each one causing a characteristic reaction. According to Panton and Valentine,¹³ different strains of staphylococci are capable of producing these toxins in varying proportions. They have also shown that while necrotoxin, hemolysin, and lethal toxin of various strains are very similar, the strains differ considerably in the production of leucocidin. The latter view has been supported by Bryce and Burnet,¹⁰ by Parish and Clark,¹⁴ and by Ramon and Richou.¹⁵

Panton and Valentine¹³ and Valentine¹⁶ have further found that acute human infections were associated with strains which produced strong leucocidin, while sycosis, acne, and other small chronic staphylococcus infections were often caused by strains which yielded powerful hemolysin but weak or undemonstrable leucocidin. In view of these findings it becomes important that toxoid used in recurrent furunculosis should be rich in leucocidin, whereas toxoid used for sycosis and similar lesions should contain powerful hemolysin. But since, at the present, there is

no differentiation made in the use of toxoid for one or another type of staphylococcus infection, it is expedient that toxoids should contain all of these toxins in sufficient quantities to stimulate the production of strong antitoxin for each individual toxin. Preferably, toxoids should be made from a number of toxigenic strains isolated from representative types of staphylococcus.

2. *Culture medium*: In order to maintain a consistently high toxigenicity of any staphylococcus, the selection of an appropriate medium is essential. The semifluid medium of Burnet¹² containing 0.8 per cent agar in the 2 per cent proteose-peptone buffered broth of Parker,⁵ seems to be widely used in this country and abroad. However, as different toxigenic strains vary in their nutritive requirements for the continuous production of powerful toxin, many modifications of this medium, in regard to the brand of peptone and meat base, have been proposed. It has been reported that the presence of a small amount of potassium, magnesium, and glucose are essential for the production of powerful toxin, some of these ingredients favoring the production of hemolysin and others of leucocidin. Ramon and his co-workers discovered many toxigenic strains by using synthetic media of definite chemical composition, including two indispensable ingredients, namely, nicotinic acid and thiamine chloride.

3. *Antitoxin Binding Power*: Burnet,¹⁷ and Ramon and his co-workers¹⁸ have found that if staphylococcus toxin and antitoxin are mixed in the proportions in which they are mutually saturated, flocculation occurs, which represents the precipitation of combined toxin and antitoxin. By means of this test it is possible to evaluate the antitoxin binding power of toxin; thereby the antigenicity of the toxin can be gauged.⁸ When toxoid is prepared by the use of formalin, the flocculation reaction remains unaltered and its antigenicity may be estimated fairly accurately quantitatively.¹⁹ These observations of Burnet, and of Ramon and his co-workers, have been confirmed by Dolman and Kitching,²⁰ Kitching and Farrell,^{21, 22} Chaudhuri,²³ and other workers, who consider the high binding power of toxoid as determined by the flocculation test most essential in the determination of the potency of toxoid. Ramon and his co-workers believed that in order to produce a beneficial therapeutic effect, toxoid must possess an antigenic power of at least 10 units per cubic centimeter, that is, that 1 c.c. of toxoid should completely flocculate 10 international units of antitoxin.

However, in the preparation of commercial toxoids this factor apparently has not always been given due attention. The study of Farrell²⁴ on eleven samples of toxoids, seven of which were obtained from the open market, proved that the number of antitoxin binding (Lb)* units of these toxoids ranged from 1.2 to 51 Lb per cubic centimeter. And out of the seven samples from the open market, five contained less than ten antitoxin binding units (Lb) per cubic centimeter.

*Lb. per cubic centimeter is the number of units of antitoxin combining with 1 ml. of toxoid.

Clinical Use of Staphylococcus Toxoid.—

1. *Connaught toxoid*: The first attempt to utilize staphylococcus toxoid in the treatment of staphylococcus infections was made in 1933, in Canada, by Dolman, who was associated with the Connaught laboratories.²⁵ Toxoid used in this work was prepared by the addition of a 0.3 per cent solution of formaldehyde to the pooled toxins obtained from several highly toxigenic strains of staphylococci, freshly isolated from various types of human lesions. When toxin was first produced it possessed very high hemolytic, dermonecrotic, and lethal power. The leucocidin power evidently was not tested. Twenty-eight patients suffering from intractable, persistent, recurrent staphylococcus infections were treated, including sixteen cases of recurrent furunculosis. Alleviation and then apparent cure followed in all cases in the course of four to eight injections, for a total of 0.75 to 1.5 ml. given at five- to seven-day intervals. The clinical improvement could be correlated with an increased titer of circulating antihemolysin, which on the average increased tenfold.

In 1935 Dolman,³¹ using Connaught toxoid, supplemented his early work with a series of 306 cases of various staphylococcus infections. In this series there were eighty-one cases of recurrent furunculosis, the others being acne, staphylococcal infections of the nose, throat, and nasal sinuses, recurrent abscesses, and fifty-nine cases of chronic osteomyelitis. He observed that the clinical evidence of the acquisition of immunity was usually apparent after two to three injections. By this time the boils showed rapid regression and new ones stopped appearing. In some cases of recurrent furunculosis, as many as twenty injections had to be given in order to prevent recurrences. In all recurrences the patients carried toxigenic strains of staphylococcus in the anterior nares. The latter finding was confirmed by Valentine.¹⁶

Gilchrist and Wilson³² successfully used Connaught toxoid in the treatment of sixty-five cases of staphylococcal infections of the upper respiratory tract in patients with diabetes, with only three failures.

2. *Burroughs Wellcome toxoid in England*: Using four injections for a total of 0.75 ml. of Burroughs Wellcome toxoid prepared in England, Connor and McKie,²⁶ Connor,²⁷ and Gohar²⁸ reported similar clinical and serologic findings in a group of patients suffering from furunculosis and sycosis. Their toxoid was prepared from the pooled toxins of four strains of staphylococci and detoxified with 0.2 per cent formaldehyde.

Similarly favorable results with Wellcome toxoid were obtained by Parish, O'Meara, and Clark²⁹ in the treatment of recurrent furunculosis. The rapid increase of the antihemolysin titer and the correlation with clinical improvement made them feel that circulating antitoxin is of value in combating the infection.

Using six injections for a total of about 2 ml. of Wellcome toxoid, Murray³⁰ reported encouraging results in a group of 116 cases of various superficial chronic staphylococcal infections. The antihemolysin titer,

which in untreated cases was usually on an average of 1 unit, reached an average of 7.6 units one week after the fourth injection. This amounted to an increase of eight times that of the initial titer. Eighty-one patients who had recovered were seen after a period of two to five months or more; in thirteen, relapses had occurred, but the lesions were usually not severe. Results in acne were less encouraging than in other infections.

Using Wellcome toxoid, Whitby^{33, 34} obtained encouraging results in a group of 200 cases. Of these, 117 were cases of furunculosis, some cases of styes, some of pustular acne, sycooses, and other superficial staphylococcal infections. Seventy-six out of 117 patients with furunculosis recovered rapidly, however, 25 per cent of these had relapses. A second course brought relief, but only continued monthly doses succeeded in preventing further relapses. There was no success in the treatment of acne and sycoosis. The variability of individual serum responses to a set dose of toxoid, and the lack of correlation between the antihemolysin titer and the clinical picture, caused Whitby to conclude that the response to antigen is a highly individual reaction.

The clinical results of Smith,³⁵ who used Wellcome toxoid in twenty cases of recurrent furunculosis, were less encouraging than the results of previous workers. Similarly to the results of Whitby, there was no correlation between antihemolysin titer and clinical results.

3. Pasteur Institute toxoid: A considerable amount of laboratory and clinical work with staphylococcus toxoid was done by the French workers Ramon, Bocage, Richau, and Mercier of the Pasteur Institute in the hospitals of Paris.³⁶⁻⁴¹ They believed that the clinical success of toxoid treatment was directly related to the degree of antigenicity of the staphylococcus toxin, from which the toxoid is derived. The antigenicity of the toxin was tested by the flocculation method applied by Ramon⁴² in testing diphtheria toxin. Several strains of staphylococci, including one freshly isolated from the blood of a patient with septicemia and another from a case of furunculosis, were used in the preparation of their toxoid. For detoxification, 0.3 to 0.5 per cent formaldehyde was used. This toxoid has been used by Ramon, Bocage, Richau, and Mercier in over 2,000 cases of various staphylococcal infections. The usual course consisted of 0.1, 0.25, 0.5, 1.0, and 2.0 ml. injections given at five-day intervals. Of 1,000 cases, mostly multiple and recurrent furuncles and carbuncles, there was rapid recovery in at least 90 per cent. When the furuncles were treated at the onset, they did not suppurate, and dried out within three to five days. Extension of furuncles in cases of multiple furunculosis usually stopped after two, and not more than three, injections. Having followed many of the cases for about four years these workers observed recurrences in only about 10 to 15 per cent of the cases. This toxoid and other similarly prepared toxoids were used widely by numerous French and other European workers.

Tzanek, Klotz, and Negreanu⁴³ treated fifty-six patients with various staphylococcal infections, with only three failures.

Excellent results were reported by Simon,⁴⁴ Debre, Bonnet, and Thieffry,⁴⁵ Decoulx and Patoir,⁴⁶ Laurent and Tardy,⁴⁷ Gaté, Guilleret, and Chanial,⁴⁸ Ungerer,⁴⁹ Moulier,⁵⁰ Soupault and Levy-Bruhl and Moulier,⁵¹ and many other workers, listed in the work of Ramon and co-workers.³⁸

Using the same preparation and technique, Rion and Bigot⁵² treated at Tonkin, 126 patients with staphylococcal infections with satisfactory results; those suffering from furunculosis usually had numerous lesions. One of these patients had had 376 boils and another 283. Both patients were greatly relieved after two injections and apparently cured after three.

Nélis,⁵³ and Nélis and van Meehelen of Belgium⁵⁴ treated sixty-five cases of furunculosis among miners, with ten injections of the same toxoid; fifty-seven of the sixty-five patients recovered rapidly.

Nélis and Piérard⁵⁵ treated a total of 300 patients and reported excellent results.

In Italy, Caminiti⁵⁶ and Perogallo⁵⁷ treated furuncles, general abscesses, and axillary abscesses with satisfactory results.

Similar reports came from Simitch and Djourichitch⁵⁸ in Belgrad, Bruck in Sweden,⁵⁹ and Montant and Dernaz in Geneva,⁶⁰ who observed that anatoxin produced the best results in axillary abscesses and acute and chronic furunculosis.

Many of these workers used the antihemolysin test as the measure of immunity and observed a rapid increase of antihemolysin titer following the toxoid injections.

Four to twenty times' increase in antihemolysin titer was observed by Mercier after a single injection of 0.5 c.c. of toxoid, and four- to thirty-five-fold increase was produced by a series of injections.

On the other hand, the antihemolysin titer of patients treated by Ramon and his co-workers³⁶ in his early work, and by Nélis and his co-workers, usually did not exceed 5 units, 2 to 3 units being the average. The original titer of their patients usually ranged between 0.25 to 1 unit.

Thus, numerous and almost consistently enthusiastic reports have come from Europe, Canada, and the French Colonies concerning the use of formaldehyde toxoid. In all cases it was prepared from the pooled toxins of several highly toxigenic strains of staphylococci obtained from various sources. Toxoid prepared at the Connaught laboratories and the Pasteur Institute was characterized by a high antigenicity, the index of which was its binding power with antitoxin as determined by the flocculation test. No information on the antitoxin binding power of Wellcome toxoid was obtained.

Contrary to these numerous and highly encouraging results on toxoid therapy in various staphylococcus infections from abroad, the reports on the use of toxoid in the United States are comparatively few, and in

which in untreated cases was usually on an average of 1 unit, reached an average of 7.6 units one week after the fourth injection. This amounted to an increase of eight times that of the initial titer. Eighty-one patients who had recovered were seen after a period of two to five months or more; in thirteen, relapses had occurred, but the lesions were usually not severe. Results in acne were less encouraging than in other infections.

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did not expedite the healing of the existing lesions, nor did it prevent the development of new ones.

Longacre⁶⁵ used pepsin digest toxoid of Lederle on thirty-five cases of various staphylococcus infections in the Vanderbilt Clinic, Columbia-Presbyterian Hospital. The majority were cases of acute and recurrent furunculosis. Some of these patients showed an immediate clinical improvement; however, when followed by us, most of them developed recurrences. There was an average increase of antihemolysin titer in the majority of these patients up to 2 to 4 units, however, no correlation was found with the clinical results.

Thus in this country, where the treatment of staphylococcus infections has met with small success, we found that the toxoid generally used has been derived by formalization or pepsin digestion of toxins of a single, or at most two, strains of staphylococci. The lesions from which these staphylococcal strains had been isolated were not similar to those in which toxoid was being applied therapeutically, and the binding power of toxoid with antitoxin as estimated by the flocculation test was either not tested as in formalin toxoid or was definitely absent as in pepsin digest toxoid.

OUR LABORATORY AND CLINICAL RESULTS WITH LEDERLE TOXOID

In collaboration with Dr. E. Howes, in 1936, we initiated the use of Lederle's formalized toxoid in the Vanderbilt Clinic. However, after having treated a group of twenty patients suffering from recurrent furunculosis, we failed to notice any marked clinical improvement in the course of treatment. We found further that the prevention of recurrences by this method in about 50 per cent of the cases was no higher than that obtained with staphylococcus stock or autogenous vaccine. It was also noted that the injections were often followed by a severe local reaction and frequently by a systemic reaction.

Our interest in toxoid was revived when the modification by the peptic digestion method of Parfentjev was introduced. The neutralization of a large proportion of protein by digestion with pepsin considerably decreased the nonspecific protein reaction and allowed for injections with larger doses of more concentrated toxoid. This study comprised a group of 200 cases of staphylococcus infections. The majority of these were cases of recurrent furunculosis, most of which had formerly proved resistant to other forms of therapy. The rest consisted of axillary abscesses, cases of acute multiple furuncles and carbuncles. A majority of the patients were treated with Lederle peptic digest toxoid alone. Some patients received a combined treatment with Lederle toxoid and autogenous vaccine* and a few were treated with vaccine alone. The

*A twenty-four-hour culture grown on a 5 per cent human blood slant, isolated from the patient's lesion, was washed with 10 c.c. of physiologic saline solution. This washing was diluted down to approximately 200 million bacteria per cubic centimeter and 0.3 per cent formaldehyde added. It was stored in the refrigerator until no growth appeared on plating.

course of toxoid injections was as follows: On the day following the skin sensitivity test, which consisted of a subcutaneous injection of 0.1 c.c. of toxoid in 1:100 dilution, 0.1 c.c. of a 1:10 dilution of toxoid was given subcutaneously. This was followed at three- to five-day intervals with 0.1, 0.25, and 0.5 c.c., and five doses of 1.0 c.c. of undiluted toxoid. In another group of cases the skin sensitivity test was done with 0.1 c.c. of undiluted toxoid and this was followed with 0.25 and 0.5 c.c. and five 1.0 c.c. doses, the total quantity being 5.85 c.c. In those cases where recurrences developed continuously despite injections, the treatment was continued for a longer period of time, depending upon the individual case. Those cases in which recurrences came following the completion of a series of injections were given a second, a third, and in some cases even a fourth series of injections.

The sera of all patients were tested for antihemolysin titer prior to the initiation of the course of injections. This testing of sera was repeated after the fourth and seventh injections and in some patients from two weeks to one month following the completion of the series. Whenever recurrences developed the serum was tested before initiating a new course. The sera of many patients were sent to the Lederle Laboratories where they were tested for antileucocidin titer, and wherever the quantity was sufficient, mouse protection tests were performed.

Out of the entire group, we are presenting only the results of those cases in which the patient received a complete course of toxoid injections and those which we were able to follow up for a period of three months to two years. The results are shown in Tables I to IV.

TABLE I

RESULTS WITH LEDERLE TOXOID SHOWING THE PERCENTAGE OF RECURRENCES IN THE TWO MAIN CATEGORIES OF TREATMENT

	TOTALS	RECURRENCES	PER CENT RECURRENCES
Recurrent furunculosis	93		
Lederle toxoid	80	49	61.3
Lederle toxoid and vaccine	10	6	60.0
Vaccine alone	3	2	66.7
Axillary abscesses	18		
Lederle toxoid	13	9	69.2
Lederle toxoid and vaccine	5	2	40.0

TABLE II

RESULTS WITH LEDERLE TOXOID SHOWING THE LACK OF CORRELATION BETWEEN THE RISE OF ANTIHEMOLYSIN AND ANTILEUCOCIDIN AND THE CLINICAL RESULT

CASE NUMBER	ANTIHEMOLYSIN		ANTILEUCOCIDIN		RECURRENCES
	BEFORE	AFTER	BEFORE	AFTER	
1	3u	10u	0.32	0.64	+
2	1u	6u	0.32	0.24	0
3	1.5u	8u	0.12	0.03	+
4	2u	4u	0.64	0.64	+
5	<1u	1u	0.15	0.2	0
6	6u	8u	0.04	0.32	±

CLINICAL RESULTS

Some cases showed immediate clinical improvement; however, these occurred in an earlier series and were very rare among the patients of the later group.

There were also many recurrences during the course of injections of Lederle toxoid. Thus, out of eighty patients with recurrent furunculosis, forty-nine developed recurrences. Of these, forty-one had recurrences following at least three injections; in twenty there were multiple recurrences. The percentage of recurrences of axillary abscesses treated with Lederle toxoid was very similar. Those treated with toxoid and vaccine gave about the same percentage of recurrences. There were no recurrences following the treatment with Lederle toxoid among five patients with acute multiple furunculosis and two with carbuncles.

SERUM ANTIHEMOLYSIN TITERS IN RECURRENT FURUNCULOSIS
TREATED WITH LEDERLE TOXOID

The antihemolysin titer before the initiation of treatment in the majority of recurrent furunculosis ranged from <1 to 1.5 units. After a series of seven or more injections, there occurred in one-half of the cases, a rise in titer to between 1 to 2.5 units, while in the other one-half it reached 3 and rarely 4 to 10 units. Thus, in only one-half of the cases did the titer reach 3 units, the level which, according to Ramon and his co-workers, affords a certain degree of protection.

A smaller number of antileucocidin and mouse protection tests were carried out,* but there was no apparent consistency in the correlation of these tests either with the rise in antihemolysin titer or in clinical results.

SKIN SENSITIVITY AND POLYSACCHARIDE TESTS

When the skin sensitivity test was run with a dilution of 1:100 of toxoid, a reaction was lacking or negligible before, during, or following the injections.

When, however, the skin sensitivity test was run with undiluted toxoid, the reaction during and following the end of treatment usually was more marked than before the treatment started. This seems to indicate a growing sensitivity to intracutaneous injections of toxoid during treatment.

Along with skin sensitivity tests, before and after injections, Julianelle's polysaccharide test was tried on the patients. However, the results were almost always negative and showed no correlation with an increase in the antihemolysin titer or with recovery.

CLINICAL AND LABORATORY RESULTS WITH CONNAUGHT TOXOID

The results obtained in recurrent staphylococcus infections with Lederle toxoid, both formalized and pepsin digested, being unsatisfac-

*In the Lederle Laboratory under the supervision of Miss Frances Clapp.

TABLE III

RESULTS WITH CONNAUGHT TOXOID SHOWING THE NUMBER AND PERCENTAGE OF RECURRENCES CORRELATED WITH THE ANTIHEMOLYSIN TITER IN RECURRENT FURUNCULOSIS

CASE NUMBER	ANTIHEMOLYSIN TITER		RECURRENCES		NOTES
	BEFORE TOXOID	AFTER 7 OR MORE INJECTIONS	DURING COURSE OF TREATMENT	WITHIN 1 YEAR AFTER TREATMENT	
1	1u	8u	0	0	Recur. after Lederle toxoid
2	2u	-	0	0	Recur. after Lederle toxoid
3	1u	8u	0	0	
4	<1u	6u	+	+	
5	1u	-	+	0	
6	1u	-	+	0	
7	1u	1u	0	0	
8	2u	4u	+	0	
9	1u	4u	+	0	
10	1.5u	8u	0	+	
11	1.5u	4u	0	0	
12	<1u	-	0	0	
13	2u	-	+	0	Diabetes
14	<1u	6u	+	0	
15	2u	3u	0	0	
16	8u	above 8u	+	+	Diabetes
17	<1u	4u	0	0	
18	1u	6u	0	0	
19	1u	-	+	0	
20	4u	8u	0	+	Recur. after Lederle toxoid
21	1u	6u	0	0	Recur. after Lederle toxoid
22	1.5u	2u	0	0	
23	1u	-	0	0	Recur. after Lederle toxoid
24	2u	-	0	0	Recur. after Lederle toxoid
25	1u	10u	+	+	Recur. after Lederle toxoid
26	1u	-	+	+	Single mild rec. in 1 month, none afterward
27	<1u	12u	0	0	
28	1u	5u	0	0	
29	1u	6u	0	0	
30	<1u	4u	0	0	
Total	30	21	11 (31.7%)	6 (20%)	

tory and inconsistent with the beneficial results reported by other workers, we felt that a similar study should be made with a toxoid yielding more favorable results in other hands.

Dr. Farrell very generously supplied toxoid made in the Connaught Laboratories in Toronto. This had been successfully used by Dolman^{25, 31} and by Gilechrist and Wilson.³² With this material, data have been obtained on an additional group of sixty-five patients.

The toxoid was given subcutaneously at five- to seven-day intervals. First dose of 0.05 c.c. was followed by 0.1, 0.15, 0.2, 0.25, 0.3, 0.4, and finally 0.5 c.c. for a total of 1.95 c.c. In the case of recurrences another series was given. Out of sixty-five patients treated, we are presenting only a group of forty patients, who received at least seven injections of toxoid and could be followed for at least one year. Of this group there were thirty cases of recurrent furunculosis and ten of recurrent axillary abscesses, alone or in combination with general furunculosis. From the accompanying Tables III and IV it is seen that recurrences during the course of the toxoid injections occurred in sixteen cases. However,

TABLE IV

RESULTS WITH CONNAUGHT TOXOID SHOWING THE NUMBER AND PERCENTAGE OF RECURRENCES CORRELATED WITH THE ANTIHEMOLYSIN TITER IN AXILLARY ABSCESSSES

CASE NUMBER	ANTIHEMOLYSIN TITER		RECURRENCES		NOTES
	BEFORE TOXOID	AFTER 7 OR MORE INJECTIONS	DURING COURSE OF TREATMENT	WITHIN 1 YEAR AFTER TREATMENT	
1	1u	2u	0	+	
2	2u	4u	+	0	
3	2.5u	4u	+	+	Recur. after Lederle toxoid
4	<1u	-	+	0	
5	<1u	4u	0	0	
6	1.5u	1u	+	+	
7	1u	6u	0	0	Recur. after Lederle toxoid
8	1u	-	0	0	
9	3.5u	5u	0	0	Recur. after Lederle toxoid
10	<1u	1.5u	+	0	
Totals	10	8	5 (50%)	3 (30%)	

after the end of the treatment there were only nine recurrences, which occurred within one year of the follow-up. Ten of the patients had been previously treated unsuccessfully with Lederle toxoid. Of these, seven recovered following the injections of Connaught toxoid. The differences between the percentages of recurrences for the Lederle and Connaught toxoids are statistically significant in favor of the Connaught toxoid.

Out of twenty-nine cases in which the antihemolysin titer was tested prior to and following a series of seven or more injections, twenty-three had 4 units or higher. In general, the serum of the patients who recovered was characterized by a high antihemolysin titer. However, there were exceptions in which recurrences developed in spite of the high titer of the antihemolysin; while in some other cases the recovery was complete in spite of the fact that the antihemolysin titer was below 3 units.

The data on the antileucocidin titer of the sera of the treated patients indicate that, although there seems to have been a slight increase following the treatment, there was no correlation with antihemolysin titer or with the clinical results. However, having complete data on only nine patients, we feel that more work should be done in order to make a definite assertion on this point.

DISCUSSION

The problem of recurrent staphylococcus infections in the form of furuncles and carbuncles frequently plagues the general practitioner and the surgeon. It is well known that certain individuals are generally resistant and others generally susceptible to infections. Others who have been resistant suddenly become susceptible. No reliable test has been discovered to measure either the resistance or the susceptibility to staphylococcus infections, although many attempts have been made

to find such a test. Normal individuals do not have a high antihemolysin titer and there must be some other element of immunity which is responsible for natural resistance. Many immunologists believe that it resides in the phagocytic power of the leucocytes, but this cannot be consistently demonstrated.

When a staphylococcus infection becomes established in the skin, local recurrences in the neighborhood suggests that the organisms get out of the original lesion and get into neighboring pores. Recurrences can be minimized by precautions taken by the patient (1) to avoid contact with the lesion by his hands, (2) to wash the hands frequently, and (3) to avoid rubbing or scratching in other areas.

The lesions themselves can frequently be aborted or their course shortened by the local injection of either penicillin or potent staphylococcus bacteriophage, and the inhibition of bacterial activity by these agents renders the organisms discharged from the lesions onto the surrounding skin less likely to gain a foothold if rubbed or scratched into other areas of the skin. This has been demonstrated in many of the cases included in this series. Neither penicillin nor bacteriophage, however, has any influence on the resistance of the individual to subsequent recurrences if there is a free interval of time after the complete subsidence of the initial infection. Therefore, the problem of building up a resistance to subsequent infections is of very great importance and must be met in some other way.

Careful analysis of the laboratory and the clinical data on staphylococcus toxoid collected by numerous workers, together with our own observations, have revealed certain factors which we feel may help practitioners and surgeons in the solution of this problem.

Favorable reports came out of Canada where Connaught Laboratory toxoid was used, and out of many European countries where toxoid prepared at the Pasteur Institute of Paris has been used. These toxoids were formaldehyde-detoxified pooled toxins of a number of toxigenic staphylococcus strains, obtained from a variety of lesions. Consequently, toxoids used in both Canada and Europe possessed multiple antigenicity. In the preparation of these toxoids the workers realized the importance of using strains isolated from lesions similar to those being treated. These strains produced strong leucocidin, which is characteristically associated with acute and severe infections. The criterion of potency of both products was a high binding power with antitoxin, which was found by many workers to be closely related to the antigenicity. This was determined by the flocculation method.

The clinical results obtained with Wellcome toxoid in England, although encouraging, seem to be on the whole less favorable than those obtained with Pasteur and Connaught toxoid. The description of their method of preparation did not disclose whether it included any strains from furunculosis or similar lesions, which produced high leucocidin. Neither was the toxoid tested for its binding power with antitoxin. The importance of the criteria of potency as applied by the French and

Canadian workers in toxoid preparation such as multiple antigenicity, high binding power with antitoxin, and consequently a rapid antibody production *in vivo*, becomes apparent when we analyze the toxoid which was used with discouraging results. Kindel and Costello, Cornbleet and Rattner, Buchman, Longacre, and we ourselves in the first group of cases used toxoid in which at least two of these criteria were not fulfilled. Toxoid was prepared from one, or at most from two, strains. Pepsin digest toxoid of Lederle possessed no binding power for antitoxin. The antigenicity was apparently not high, since of a group of six patients treated by Dr. A. Coca at the Lederle Laboratories, only one "who had an average of seven injections of toxoid, reached an antihemolysin titer of $\frac{1}{4}$ units, the remaining five reaching a maximum of 2 units."⁶⁹ Similar titers were obtained following seven injections in our group of patients treated with Lederle pepsin digest toxoid. A desire to eliminate nonspecific protein reactions, local as well as systemic, led to the introduction of the pepsin digest process for the conversion of toxin into toxoid. Apparently, however, the pepsin digestion resulted in a decrease of the antigenicity of toxoid for human beings although the antihemolysin titer in rabbits did not significantly differ from the one produced by the formalized product. Besides, the persistence of a still significant local reaction seems to indicate that although practically all the protein was neutralized by digestion with pepsin, an incomplete detoxification occurred. This is shown by the appearance of hemolysis of rabbit blood cells after overnight standing and an extremely severe reaction when toxoid containing Lyons' strain, which produced strong leucocidin, was included in the preparation of toxoid.

As to the mechanism of the action of toxoid therapy: Is its role only to stimulate the production of antitoxin against hemolysin, leucocidin, and dermonecrotizing toxin?

Undoubtedly the production of antitoxin is an essential factor in inducing immunity. This has been shown by many animal experiments in which protection against living staphylococci was attained by toxoid injections but not by vaccine injections.

Toxoid also contains nonspecific proteins which may induce a reaction similar to the nonspecific protein shock therapy.

There are also nonspecific defense factors of the body, particularly phagocytoses, which were reported to have been stimulated by the increase of antitoxin to the blood. It should also not be forgotten that toxoid contains bacterial antigens stimulating the production of bacteriotropins, agglutinins, and bacteriolysins.

However, if these bacterial antibodies are to be of value in combating the causative organisms, they must be stimulated by a strain closely related to that producing the lesion. In testing bacteriophage susceptibility of staphylococci isolated from various lesions, we have found that strains possessing the same morphologic and biologic characteristics differed in their phage susceptibility according to their source and the duration of infection.

Thus staphylococci, isolated from acute osteomyelitis, were more susceptible to phage than those of chronic osteomyelitis. The staphylococci causing conjunctivitis or sinusitis displayed only partial susceptibility to phage, while staphylococci isolated from acute infections such as furunculosis or septicemia were completely susceptible in 95 per cent of the cases. However, if phage was adapted to one strain from a case of sinusitis it was often found to become completely effective against the majority of strains from similar lesions. The same was found to be true with cases of conjunctivitis. It is our belief, following these observations, that in order to be effective against one or another type of infection, toxoid should necessarily include toxigenic strains of bacteria isolated from lesions similar to those being treated. It is possible that the success of Thygeson in the toxoid therapy of chronic blepharoconjunctivitis might be partially attributed to a closer antigenic relationship between the strain used in toxoid preparation and the strains causing this infection. It might also be attributed to the production by the Wood strain of a powerful hemolysin, which is likely to be characteristic of staphylococci causing this infection.^{13, 16}

The antibacterial body antigen which is comparatively scarce in toxoid might be better supplied in the form of vaccines. Analysis of clinical results obtained with staphylococcus pepsin digest toxoid in the Vanderbilt Clinic have shown that the therapeutic effect of this preparation was unsatisfactory. Considering that a certain percentage of patients with recurrent furunculosis recover spontaneously, the recurrences in forty-nine out of eighty cases of recurrent furunculosis and in nine out of thirteen cases of axillary abscesses seem to be indicative of the lack of the therapeutic value of that toxoid. This conclusion seems to have been further supported by the uninterrupted recurrences during treatment in many of the cases. An increase of the skin reaction following the course of injections of toxoid seemed even to indicate an increased sensitivity to toxoid, which was possibly caused by the modification of protein by pepsin digestion.

Furthermore, we feel that in spite of a frequent correlation of high antihemolysin with clinical success, it is not the antihemolysin titer which determines the state of immunity, but rather that an increase in antihemolysin parallels a raise of antileucocidin, which is the more important factor in immunity against staphylococci causing recurrent furunculosis. Unfortunately, however, the present technique of the antileucocidin test as described by Valentine does not allow clear-cut results. A certain amount of destruction of the leucocytes, due to manipulations in obtaining a concentrated leucocyte suspension, makes the microscopic interpretation of the results extremely difficult and uncertain. A simple test, perhaps on the line of the Parker Weld⁷⁰ leucocyte agglutination test, might be used for the measurement of the antileucocidin power.

It has been the experience of many workers that clinical success in staphylococcus infections is most frequently associated with a sharp and immediate rise of antihemolysin titer, rather than a slow prolonged course in reaching the same level. We feel that in those cases where a very slow rise of blood titer necessitated a prolonged treatment, along with an increased immunity to exotoxins, there may have developed a hypersensitivity to bacterial proteins.

SUMMARY

1. The treatment of ninety-three patients with recurrent furunculosis and axillary abscesses with Lederle's pepsin digest toxoid resulted in a complete recovery of only 38 per cent. In the other 62 per cent, recurrences developed within one year after the end of the treatment.

2. Of the seventy patients who received at least seven injections of Lederle's pepsin digest toxoid, the antihemolysin titer in fifty-two cases (74 per cent) ranged between 1 and 3 units and in eighteen (26 per cent) it was between 3 and 10 units.

3. Out of forty patients with recurrent furunculosis and axillary abscesses treated with Connaught toxoid, complete recovery occurred in thirty-one (78 per cent). Nine others (22 per cent) developed recurrences within one year after the end of the treatment. In five of the cases the recurrences were milder than prior to the treatment.

4. Of twenty-nine patients tested following seven or more injections of Connaught toxoid, the antihemolysin titer of the sera in twenty-three (79 per cent) ranged between 4 and 12 units; only in six (21 per cent) was it 3 units or less. These are statistically significant differences.

5. The antihemolysin test is not a strict measure of immunity, for there are exceptional cases in which the patient has a rise in titer and has recurrences, and others who have no rise and yet seem to be cured.

7. There may be some other immune factor which does not run strictly parallel with the antihemolysin titer which is of major importance but cannot be measured.

CONCLUSIONS

Staphylococcus toxoid, made from toxigenic strains, is able, by means of repeated injections, to increase the antihemolysin titer of the blood and to lessen significantly the incidence of recurrence of furuncles and carbuncles.

REFERENCES

1. Van de Velde, H.: *Cellule* 10: 401, 1894.
2. Lingelsheim, W. Von: *Beitr. z. exper. Therap.* 1: 49, 1899.
3. Kraus, R., and Clairmont, W.: *Wien. klin. Wchnschr.* 13: 49, 1900.
4. Kraus, R., and Pribram, E.: *Wien. klin. Wchnschr.* 19: 493, 1906.
5. Parker, J. T.: *J. Exper. Med.* 40: 761, 1924.
6. Parker, J. T., Hopkins, J. G., and Gunther, A.: *Proc. Soc. Exper. Biol. & Med.* 54: 315, 1931.
7. Parker, J. T., and Gunther, A.: *J. Exper. Med.* 54: 315, 1931.
8. Burnet, F. M.: *J. Path. & Bact.* 32: 717, 1929.
9. Idem: *J. Path. & Bact.* 33: 1, 1930.

10. Bryce, L. M., and Burnet, F. M.: *J. Path. & Bact.* 35: 183, 1932.
11. Glenn, H. T., and Stevens, M. F.: *J. Path. & Bact.* 40: 201, 1935.
12. Burnet, F. M.: *J. Path. & Bact.* 34: 471, 1931.
13. Panton, P. A., and Valentine, F. C.: *Lancet* 1: 506, 1932.
14. Parish, H., and Clark, W. H. M.: *J. Path. & Bact.* 35: 251, 1932.
15. Ramon, G., and Richou, R.: *Compt. rend. Soc. de biol.* 121: 379, 1936.
16. Valentine, F. C.: *Lancet* 1: 526, 1936.
17. Burnet, F. M.: *J. Path. & Bact.* 34: 471, 1931.
18. Ramon, G., Nélis, P., and Bonnet, H.: *Compt. rend. Soc. de biol.* 119: 787, 1935.
19. Ramon, G., Bonnet, H., Nélis, P., Richou, R., and Thieffry, S.: *Compt. rend. Soc. de biol.* 119: 790, 1935.
20. Dolman, C. E., and Kitching, J. S.: *J. Path. & Bact.* 41: 37, 1935.
21. Kitching, J. S., and Farrell, L. N.: *Am. J. Hyg.* 24: 268, 1936.
22. Kitching, J. S., and Farrell, L. N.: *J. Immunol.* 33: 1, 1938.
23. Chaudhuri, N.: *Calcutta M. J.* 35: 177, 1939.
24. Farrell, L. N.: *J. Immunol.* 41: 119, 1941.
25. Dolman, C. E.: *J. A. M. A.* 100: 1007, 1935.
26. Connor, J. I., and McKie, M.: *Brit. J. Dermat.* 1: 1054, 1934.
27. Connor, J. I.: *Brit. M. J.* 2: 1195, 1935.
28. Gohar, M.: *J. Trop. Med.* 38: 259, 1936.
29. Parish, H. S., O'Meara, R. A., and Clark, W. H.: *Lancet* 1: 1054, 1934.
30. Murray, D. S.: *Lancet* 1: 303, 1935.
31. Dolman, C. E.: *Lancet* 1: 306, 1935.
32. Gilchrist, J., and Wilson, M.: *Canad. M. A. J.* 30: 353, 1934.
33. Whitby, L. E.: *Lancet* 2: 779, 1934.
34. Whitby, L. E.: *Lancet* 1: 1454, 1936.
35. Smith, J. Ferguson: *Brit. J. Dermat.* 48: 84, 1936.
36. Ramon, G., Bocage, A., Richau, R., and Mercier, P.: *Presse méd.* 43: 1137, 1935.
37. Ramon, G., Bocage, A., Richau, R., and Mercier, P.: *Presse méd.* 44: 185, 1936.
38. Ramon, G., Bocage, A., Mercier, P., and Richau, R.: *Presse méd.* 44: 185, 1936.
39. Mercier, P.: *These*, 1937.
40. Ramon, G.: *Arch. de méd. d. enf.* 41: 665, 1938.
41. Bocage, A., Mercier, P., and Richau, R.: *Presse méd.* 47: 243, 1939.
42. Ramon, G.: *Comp. rend. Acad. d. Sc.* 177: 1338, 1923.
43. Tzanck, A., Klotz, H., and Negreanu, A.: *Bull. et mém. Soc. méd. d. hôp. de Paris* 52: 352, 1936.
44. Simon, C.: *Bull. méd.* 13: 219, 1936.
45. Debre, R., Bonnet, H., and Thieffry, S.: *Paris méd.* 1: 494, 1936.
46. Decoulx, P., and Patoir, G.: *Echo méd. du Nord* 8: 445, 1937.
47. Laurent, C., and Tardy: *Loire méd.*, No. 5, 140, 1936.
48. Gaté, J., Cuilleret, P., and Chaniat, G.: *J. de méd. de Lyon* 17: 381, 1936.
49. Ungerer, G.: *These Strassbourg*, 1937.
50. Moulier, S.: *These Paris*, 1937.
51. Soupault, R., Levy-Bruhl, M., and Moulier, S.: *Paris méd.* 2: 133, 1937.
52. Riou, M., and Bigot, A.: *Bull. Soc. méd.-chir. de l'Indochine* 14: 997, 1936.
53. Nélis, P.: *Presse méd.* 43: 1141, 1935.
54. Nélis, P., and van Mechelen, V.: *Rev. d'hyg.* 58: 729, 1936.
55. Nélis, P., and Piéard, J.: *Bruxelles-méd.* 17: 412, 502, 1937.
56. Caminiti, S.: *Atti e Mim. d' acc. Med. Lomb. Sez. di Chir.* No. 5, 183, 1936.
57. Peragallo, F.: *Boll. d' est. Sieroterap. Milanese* 16: 582, 1937.
58. Simitch, T., and Djuurichitch, M.: *Acta Pathologica* 2: 1, 1938.
59. Brück, Constant: *Nord. med.* 6: 1108, 1940.
60. Montant, R., and Dernaz, G.: *Schweiz. med. Wchnschr.* 67: 1184, 1937.
61. Kindel, D., and Costello, M.: *J. A. M. A.* 102: 1787, 1934.
62. Cornbleet, T., and Rattner, H.: *J. A. M. A.* 102: 780, 1934.
63. Tanenbaum, S., Joyner, A., Speed, J., and Bremer, K.: *J. Allergy* 9: 241, 1938.
64. Thygeson, P.: *Arch. Ophth.* 20: 271, 1938.
65. Thygeson, P.: *Arch. Ophth.* 26: 430, 1941.
66. Julianelle, L., Boots, R., and Harrison, G.: *Am. J. Ophth.* 25: 431, 1942.
67. Buchman, J.: *J. A. M. A.* 108: 1151, 1937.
68. Longacre, A.: *SURGERY* 10: 576, 1941.
69. Parfentjev, I., Clapp, E., and Waldschmidt, A.: *J. Immunol.* 40: 189, 1941.
70. Weld, J. P., and Mitchell, L.: *Proc. Soc. Exper. Biol. & Med.* 49: 370, 1942.

PLASTIC SURGERY IN RECONSTRUCTING ENLARGED BREASTS

ONE-STAGE MASTOPEXY

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THE plastic surgeon is often called upon to reconstruct enlarged and deformed breasts. With such deformity, aside from mental embarrassment, the patient suffers from physical disability. The posture is poor, the shoulders are rounded, shoulder strap marks are painful, and the excess weight of the breasts enervates the individual.

Numerous papers have reviewed the literature and discussed the evolution of the surgical methods.^{2, 3, 6, 7} It is our purpose to evaluate the end results of several procedures so that their applicability to the specific case may be judged. Two factors must be thoroughly understood in order to appraise the method of approach: (1) the anatomy and physiology of the breast and (2) the type of deformity and pathology involved.

SURGICAL ANATOMY AND PHYSIOLOGY

Embryology.—Early in the development of many mammals a slight ectodermal ridge appears along the side running from the axilla to the groin. As the embryo develops these ridges disappear into a series of pyramids, each forming a slight elevation and constituted of ectodermal cells. These are the anlagen of the future mammary glands. In the human being, they are always in excess to the number of mammary glands normal to the species. However, should an extra one persist, a supernumerary breast occurs, while if there is a suppression of all these anlagen, there is an absence of the mammary gland. Should a suppression occur on one side, then only one normal breast will develop.

The mammary gland may be regarded as analogous to the sweat gland. Commencing as a stalklike growth in the derma, it envelops its way into the superficial fascia. It then develops several branches which extend in various directions, push deeper, and finally rest on the covering of the pectoralis major muscle. Most of the fat, therefore, comes to lie between the glandular structure and the skin. Thus, in early youth the breast is shaped by the adipose tissue.

Blood Supply.—Superiorly, the mammary gland receives its circulation from the axillary artery which gives off the pectoral branch of the acromial thoracic artery at the inner border of the pectoralis minor muscle. It descends between the pectoralis major and minor, anastomosing with the intercostals and the long thoracic artery. Medially, the breast is supplied by the perforating branches of the internal

Presented in abridged form in conjunction with colored surgical motion pictures at the Los Angeles County Medical Association, May 11, 1944.

Received for publication, July 3, 1944.

10. Bryce, L. M., and Burnet, F. M.: *J. Path. & Bact.* 35: 183, 1932.
11. Glenny, H. T., and Stevens, M. F.: *J. Path. & Bact.* 40: 201, 1935.
12. Burnet, F. M.: *J. Path. & Bact.* 34: 471, 1931.
13. Pantou, P. A., and Valentine, F. C.: *Lancet* 1: 506, 1932.
14. Parish, H., and Clark, W. H. M.: *J. Path. & Bact.* 35: 251, 1932.
15. Ramon, G., and Richou, R.: *Compt. rend. Soc. de biol.* 121: 379, 1936.
16. Valentine, F. C.: *Lancet* 1: 526, 1936.
17. Burnet, F. M.: *J. Path. & Bact.* 34: 471, 1931.
18. Ramon, G., Nélis, P., and Bonnet, H.: *Compt. rend. Soc. de biol.* 119: 787, 1935.
19. Ramon, G., Bonnet, H., Nélis, P., Richou, R., and Thieffry, S.: *Compt. rend. Soc. de biol.* 119: 790, 1935.
20. Dolman, C. E., and Kitching, J. S.: *J. Path. & Bact.* 41: 37, 1935.
21. Kitching, J. S., and Farrell, L. N.: *Am. J. Hyg.* 24: 268, 1936.
22. Kitching, J. S., and Farrell, L. N.: *J. Immunol.* 33: 1, 1938.
23. Chaudhuri, N.: *Calcutta M. J.* 35: 177, 1939.
24. Farrell, L. N.: *J. Immunol.* 41: 119, 1941.
25. Dolman, C. E.: *J. A. M. A.* 100: 1007, 1935.
26. Connor, J. I., and McKie, M.: *Brit. J. Dermat.* 1: 1054, 1934.
27. Connor, J. I.: *Brit. M. J.* 2: 1195, 1935.
28. Gohar, M.: *J. Trop. Med.* 38: 259, 1936.
29. Parish, H. S., O'Meara, R. A., and Clark, W. H.: *Lancet* 1: 1054, 1934.
30. Murray, D. S.: *Lancet* 1: 303, 1935.
31. Dolman, C. E.: *Lancet* 1: 306, 1935.
32. Gilchrist, J., and Wilson, M.: *Canad. M. A. J.* 30: 353, 1934.
33. Whitby, L. E.: *Lancet* 2: 779, 1934.
34. Whitby, L. E.: *Lancet* 1: 1454, 1936.
35. Smith, J. Ferguson: *Brit. J. Dermat.* 48: 84, 1936.
36. Ramon, G., Bocage, A., Richau, R., and Mercier, P.: *Presse méd.* 43: 1137, 1935.
37. Ramon, G., Bocage, A., Richau, R., and Mercier, P.: *Presse méd.* 44: 185, 1936.
38. Ramon, G., Bocage, A., Mercier, P., and Richau, R.: *Presse méd.* 44: 185, 1936.
39. Mercier, P.: *These*, 1937.
40. Ramon, G.: *Arch. de méd. d. enf.* 41: 665, 1938.
41. Bocage, A., Mercier, P., and Richau, R.: *Presse méd.* 47: 243, 1939.
42. Ramon, G.: *Comp. rend. Acad. d. Sc.* 177: 1338, 1923.
43. Tzanek, A., Klotz, H., and Negrenau, A.: *Bull. et mém. Soc. méd. d. hôp. de Paris* 52: 352, 1936.
44. Simon, C.: *Bull. méd.* 13: 219, 1936.
45. Debre, R., Bonnet, H., and Thieffry, S.: *Paris méd.* 1: 494, 1936.
46. Decoulx, P., and Patoir, G.: *Echo méd. du Nord* 8: 445, 1937.
47. Laurent, C., and Tardy: *Loire méd.*, No. 5, 140, 1936.
48. Gaté, J., Cuilleret, P., and Chanial, G.: *J. de méd. de Lyon* 17: 381, 1936.
49. Ungerer, G.: *These Stransbourgh*, 1937.
50. Moulrier, S.: *These Paris*, 1937.
51. Soupault, R., Levy-Bruhl, M., and Moulrier, S.: *Paris méd.* 2: 133, 1937.
52. Riou, M., and Bigot, A.: *Bull. Soc. méd.-chir. de l'Indochine* 14: 997, 1936.
53. Nélis, P.: *Presse méd.* 43: 1141, 1935.
54. Nélis, P., and van Mechelen, V.: *Rev. d'hyg.* 58: 729, 1936.
55. Nélis, P., and Piéard, J.: *Bruxelles-méd.* 17: 412, 502, 1937.
56. Caminiti, S.: *Atti e Mim. d' acc. Med. Lomb. Sez. di Chir.* No. 5, 183, 1936.
57. Peragallo, F.: *Boll. d' est. Sieroterap. Milanese* 16: 582, 1937.
58. Simitch, T., and Djuurichitch, M.: *Acta Pathologici* 2: 1, 1938.
59. Brück, Constant: *Nord. med.* 6: 1108, 1940.
60. Montant, R., and Dernaz, G.: *Schweiz. med. Wehnschr.* 67: 1184, 1937.
61. Kindel, D., and Costello, M.: *J. A. M. A.* 102: 1787, 1934.
62. Cornbleet, T., and Rattner, H.: *J. A. M. A.* 102: 780, 1934.
63. Tanenbaum, S., Joyner, A., Speed, J., and Bremer, K.: *J. Allergy* 9: 241, 1938.
64. Thygeson, P.: *Arch. Ophth.* 20: 271, 1938.
65. Thygeson, P.: *Arch. Ophth.* 26: 430, 1941.
66. Julianelle, L., Boots, R., and Harrison, G.: *Am. J. Ophth.* 25: 431, 1942.
67. Buchman, J.: *J. A. M. A.* 108: 1151, 1937.
68. Longacre, A.: *SURGERY* 10: 576, 1941.
69. Parfentjev, I., Clapp, F., and Waldschmidt, A.: *J. Immunol.* 40: 189, 1941.
70. Weld, J. P., and Mitchell, L.: *Proc. Soc. Exper. Biol. & Med.* 49: 370, 1942.

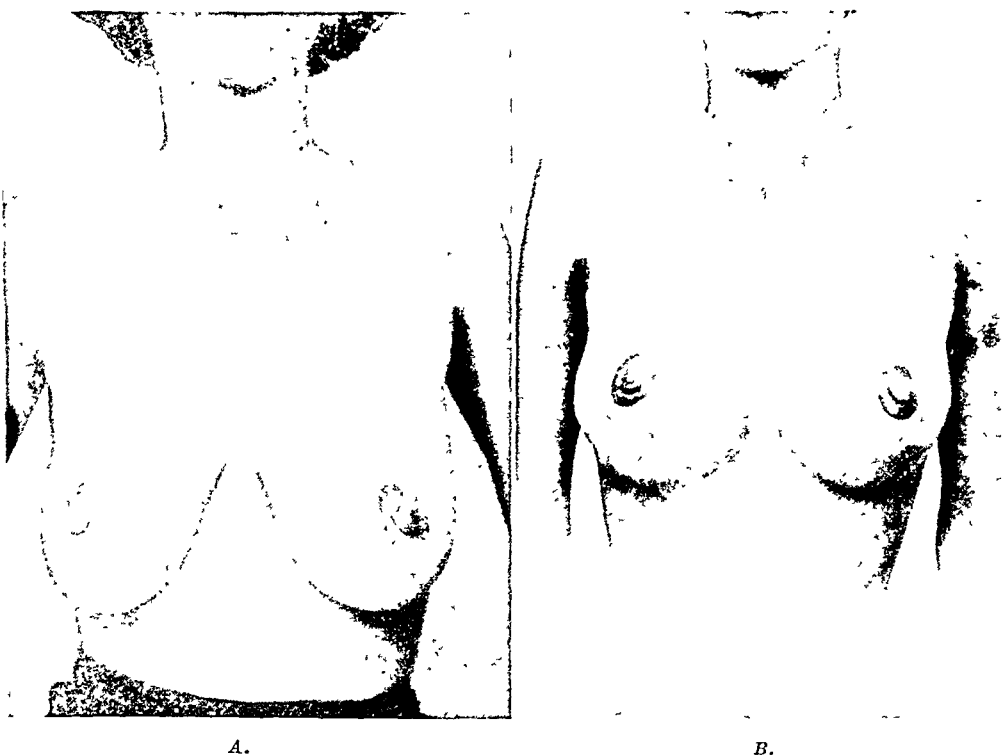


Fig. 1.—One-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification: A and C, Pendulous breasts with enlarged areola. The type of deformity and youth of the patient make this case ideal for the method. B and D, Symmetry of the breasts, the desired anteroposterior dimensions, the required areolar size, and the normal position of the nipple have been attained. The functional physiology is undisturbed. The inverted T-shaped scar blends with the breast contour.

fatty globules. Connective tissue surrounds each duct. The fibrous tissue also forms a support for the blood vessels, lymphatics, and parenchyma. In a lactating breast the gland structure enlarges; in turn the fibrous tissue stretches to accomodate the increase. There is a loss of fat and, consequently, a tendency for the breast to increase in size and become pendulous following this physiologic process.

EVALUATION OF THE DEFORMITY

Etiology.—Several factors may contribute to breast enlargement. Of these, heredity stands foremost. Pregnancy and lactation undoubtedly serve to distort breast contour. However, it is not uncommon to see many multiparae with one or even several children who have retained small contoured breasts.



A.

B.

Fig. 2.—*One-Stage Mastopexy With Transposition of the Nipple.* . . . *Author's Modification:* A, Enlarged, asymmetrical breasts with the right breast extending $3\frac{1}{2}$ cm. lower than the left. This type of asymmetry is not uncommon. B, The breast has been surgically reconstructed and the function retained.

Improper support may serve as an element in stimulating pendulous breasts. The binding brassière often acts to increase the ptosis. Lack of reasonable support during and after pregnancy may allow the breasts to prolapse premanently due to their excess weight.

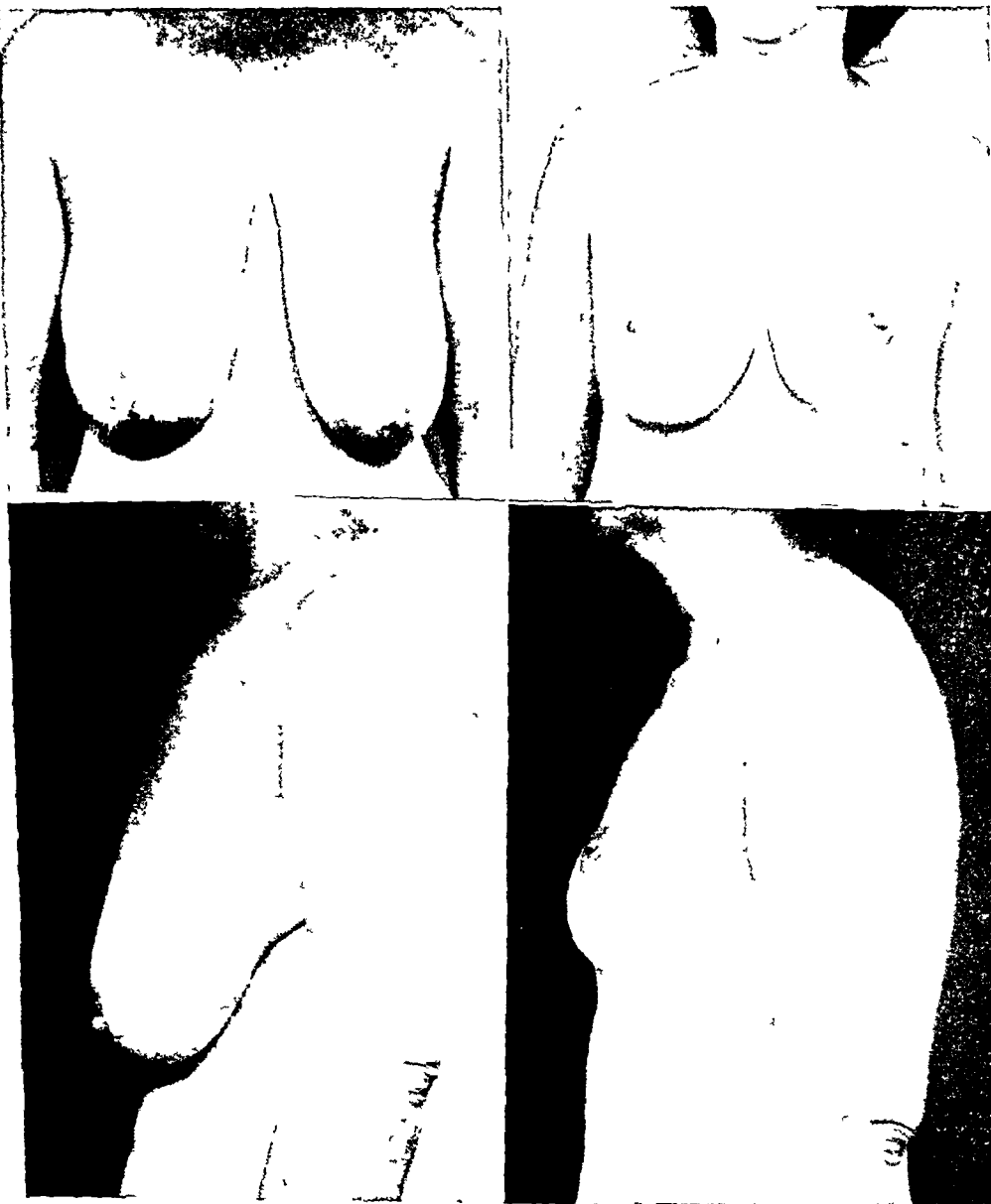
Endocrine disturbances often lead to lax, pendulous mammary glands.⁴

Mechanism of the Deformity.—Many patients with hypertrophied, pendulous breasts present a history of steady gradual enlargement

dating from puberty. Those cases with small saclike dependent breasts usually elicit a history of their occurrence following pregnancy or excessive weight reduction. In these latter cases, there has been little absolute increase in fatty tissue, but rather an elongation of the glandular stalk,

A.

B.



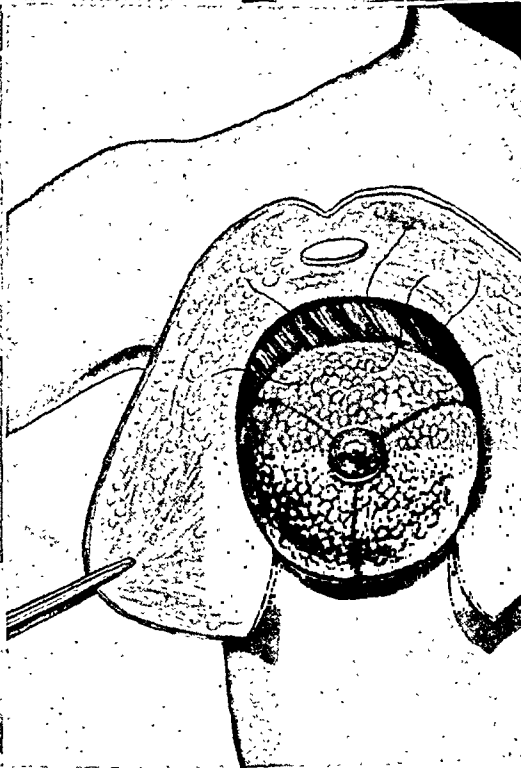
C.

D.

Fig 3.—One Stage Mastopexy With Transposition of the Nipple . . . Author's Modification: A and C, Pendulous breasts with large areola. The patient presented poor posture, rounded shoulders, deep red shoulder strap marks, and great mental embarrassment. B and D, Patient returned to work in three weeks and photographs were taken six weeks after surgery.

A.

B.



C.

D.

Fig. 4.—(For legend see opposite page.)

allowing the breast tissue to descend lower on the thorax with resultant stretching of the skin.

Measurements.—Numerous methods of gauging the new location of the nipple and breast have been evolved. These techniques have been well described⁸ and the specific choice will depend upon the individual surgeon. Regardless of the procedure employed for measurements, the position of the nipple and breast will vary depending upon the size of the individual and the deformity encountered.

It is important to place the breast up to its theoretical position in order to gauge the new nipple location and the amount and areas of breast tissue to be removed. The reconstructed areola should not be created too small and its size should coincide with the newly constructed breast.

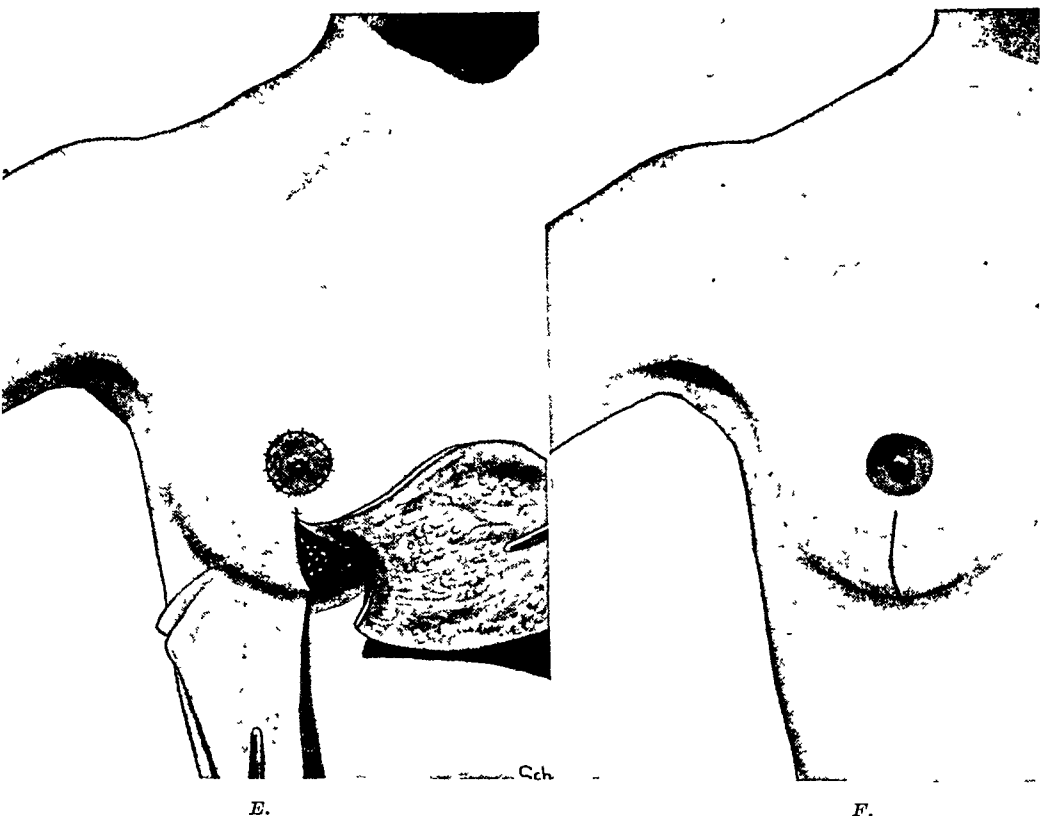


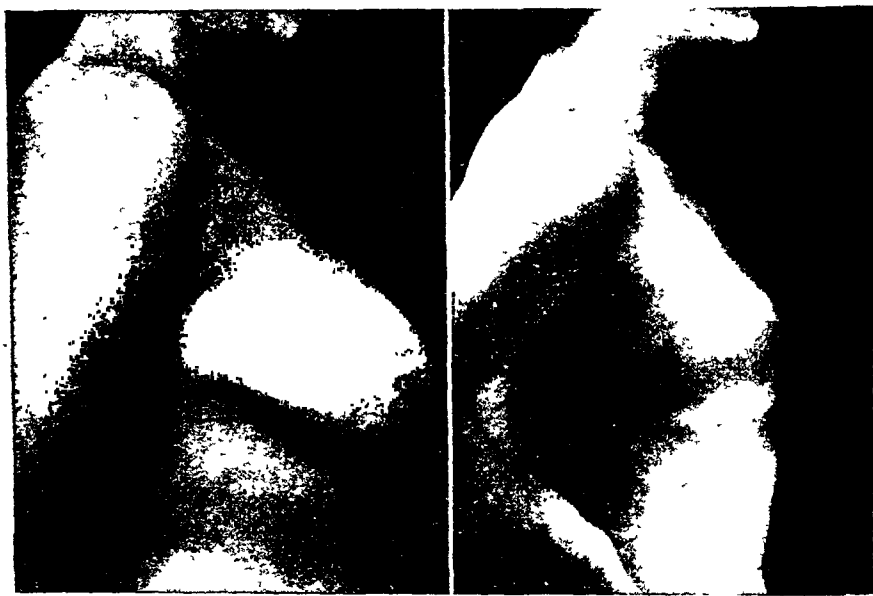
Fig. 4.—Illustrations Depicting Author's Modification of the One-Stage Mastopexy: *A*, The lines of incision have been carefully measured and marked, indicating the new position of the nipple, the amount of areola to be transferred, and the size of the skin flaps. *B*, The skin is undermined in a thick flap. The nipple and its required amount of areola are left attached to the completely denuded breast. Triangular wedges of tissue are marked off to be resected with respect to the circulation. A circular button of skin is excised to create the new nipple site. *C*, The wedges of breast tissue are resected, removing the required amount that will allow the reconstruction of a breast with the desired size, shape, and symmetry. *D*, The breast tissue is united with silk and the upper pole is fixed to the pectoral fascia over the second rib with heavy silk sutures. *E*, The areola is sewn into its new residence. The skin flaps are so cut as to adjust themselves to the new size, contour, and position of the breast. *F*, The wound edges of the inverted T incision are sewn with interrupted silk sutures.

Classification.—Gillies and McIndoe³ have classified breast hypertrophies into the following types:

1. Long heavy pendulous breasts with hypertrophy of the most dependent glandular portion. This type probably is a resultant of both endocrine and congenital causes.

2. Broad, heavy breasts associated with obesity and exacerbated by pregnancy. This type, too, may be both endocrine and congenital.

3. Saclike dependent breasts which may follow obesity reduction, multiple pregnancies, or age.



A.

B.

Fig. 5.—*One-Stage Mastopexy With Transposition of the Nipple . . . Author's Modification:* A. This patient, para iii, referred for surgery by her internist, suffered from mental embarrassment. B. This proved an ideal case for surgery, from both the standpoint of cooperation of the patient and the psychologic result.

4. True gynecomastia, with marked hypertrophy of the glandular elements of the breast resulting in enormous enlargement.

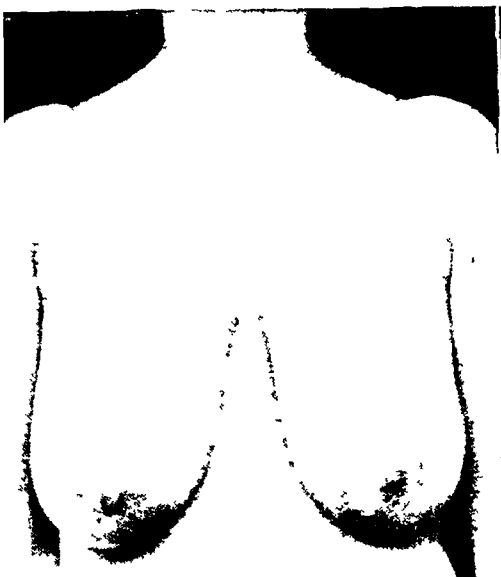
5. Asymmetry, which may vary from complete suppression of one breast to normalcy of one and excessive enlargement of its partner.

SURGICAL METHODS

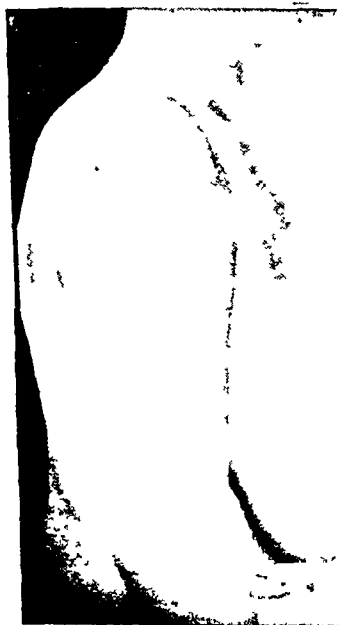
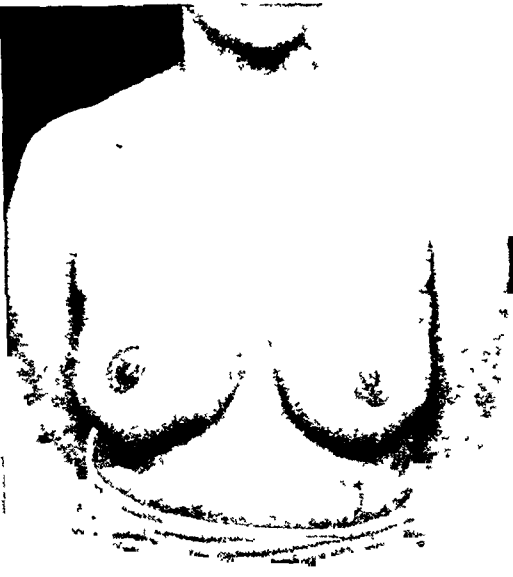
During the last half century, various surgical procedures for mastopexy have been described. The evolution of surgical techniques has been classically reviewed by Thorek.⁸ As the methods of procedure advanced, the operation for mastopexy developed from merely a removal of excess skin to a complete reconstruction of the breast. Until the last two decades, the method had one common defect. The breasts were

made somewhat smaller, but contour, symmetry, and shape were ignored. Often the procedures utilized were applicable for reconstruction of smaller breast deformities only. When large pendulous breasts were encountered with third degree ptosis, two and three stages were required and the results were often found wanting.

A.



B.



C.



D

Fig 6—One Stage Mastopexy With Transposition of the Nipple . . . Author's Modification: A and C, Enlarged asymmetrical breasts associated with poor posture and marked physical discomfort; para 1, with functional breasts. B and D, Reconstruction of the breasts and transposition of the areola with retention of physiologic function. Patient has recently had a second child.

We believe that no single surgical method should be applied to all cases, but rather the surgeon should vary the approach with the existing deformity.

We divide the surgical methods into three categories:

1. *One-Stage Mastopexy With Transposition of the Nipple:* Modified after Joseph, Lexer, Kraske, Noel, Beisenberger, Schwartzman, Gillies, and McIndoe. (Figs. 1 through 9.)

2. *Two-Stage Mastopexy With Nipple Transplant:* Modified after Thorek and Updegraff. (Figs. 10 through 13.)

3. *Two-Stage Mastopexy With Transposition of the Nipple:* Modified after Morestin, Villandre, Lotsch, Passot, Axenhausen, and Defermontel. (Figs. 14 through 16.)



Fig. 7.—*One-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* A, Pendulous hypertrophied breasts with excess fatty tissue causing physical debilitation. B, The scars following surgery are longer in this case because of the initially large breasts.

SURGICAL TECHNIQUE

One-Stage Mastopexy With Transposition of the Nipple

The one-stage operation with transposition of the nipple may be used in the majority of patients with enlarged, hypertrophied breasts. The method allows for breast reconstruction with the desired symmetry, size, and shape in conjunction with retention of its functional physiology.

Author's Modification.—The patient is placed on the table in a semi-Fowler position with the arms akimbo. The anesthesia is usually intratracheal.

The lines of incision which have been carefully measured and marked the previous day are remarked. The initial incision is circular around the areola. From the center edge of this incision another is made

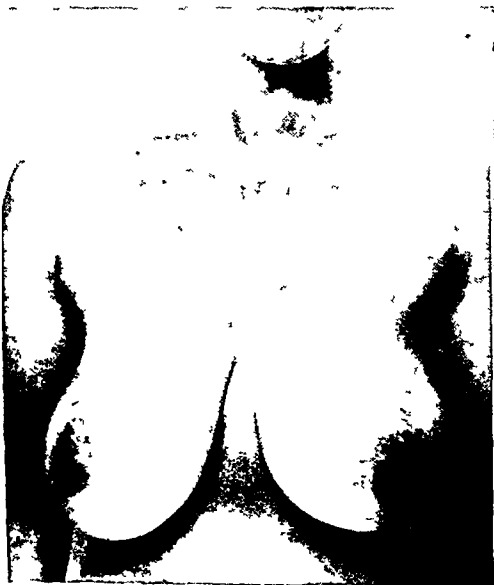


A.

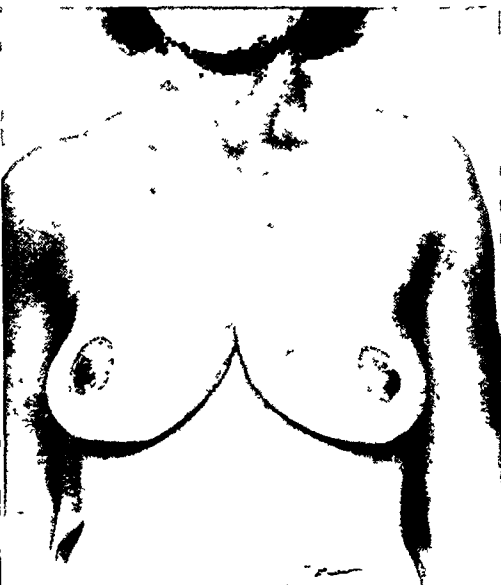


B.

Fig. 8.—*One Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* A, Long, heavy, pendulous breasts in a younger woman, probably of congenital and endocrine origin. The ptosis resulted in mental and physical discomfort. B, Surgical reconstruction with the cross of the inverted T incision well concealed by the normal position of the lower pole of the breast, while the handle of the incision may be seen running from the areola downward.



A.



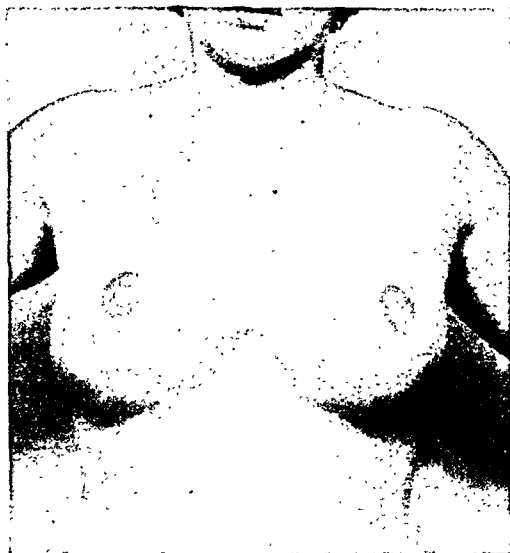
B.

Fig. 9.—*One Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* A, Because of the marked hypertrophy, this case may have lent itself better to a two-staged operation. B, The one-stage procedure proved quite satisfactory.



A.

B.



C.

Fig. 10.—*Two-Stage Mastopexy With Nipple Transplant. . . . Author's Modification After Thorek:* A, Marked hypertrophy associated with a nonfunctional breast necessitated a two-stage operation. The surgeon's discretion is used in choosing the type of two-stage operation to be employed. B, Following careful measurements to ascertain the new position of the nipple and the desired size, contour, and symmetry of the contemplated breast, the former is transplanted to its new residence. C, Two weeks afterward, the required amount of breast tissue is resected by removing triangular wedges. The skin flaps are adjusted, the wound edges are approximated in the form of an inverted T and sewed with interrupted silk sutures.

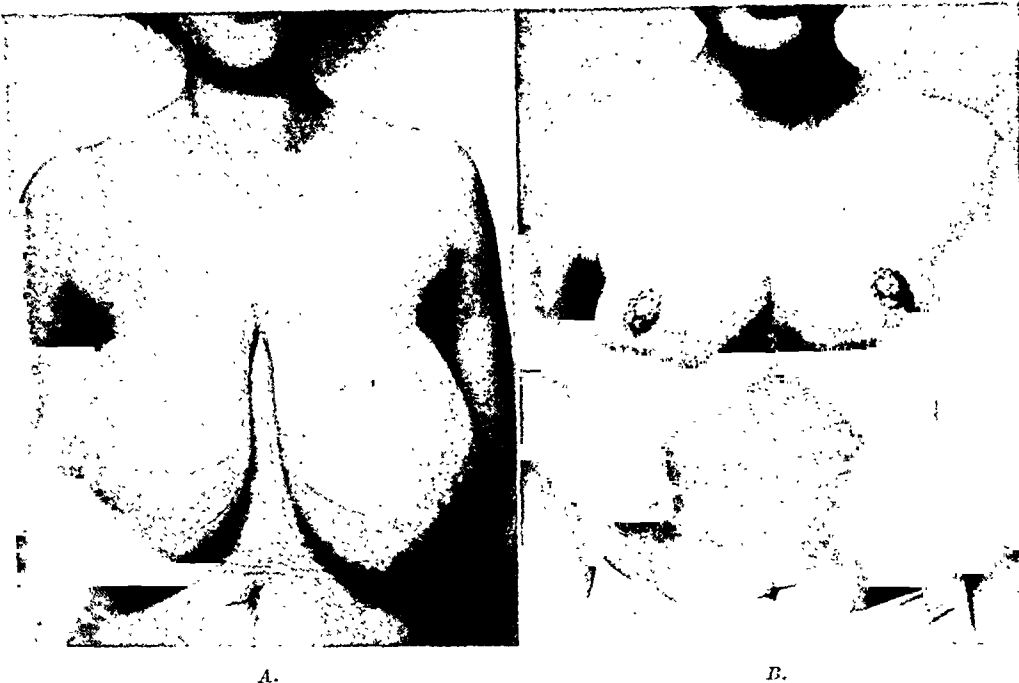


Fig. 11.—*Two-Stage Mastopexy With Nipple Transplant. . . . Author's Modification After Thorek:* *A*, Generalized breast hypertrophy in a young girl associated with nonfunction. The conditions present required two-stage operation for reconstruction. *B*, Two months following the second stage operation: the nipple transplants have taken well and the breasts have been reconstructed to the required size, shape, and symmetry.



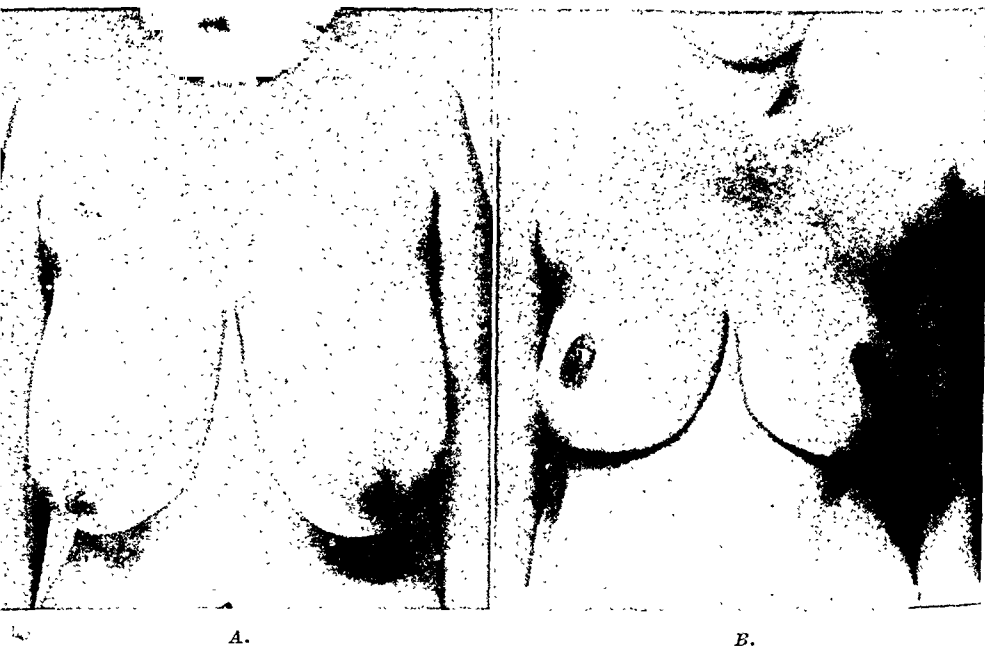
Fig. 12.—*Two-Stage Mastopexy With Nipple Transplant. . . . Author's Modification After Thorek:* *A*, Nonfunctional markedly hypertrophied breasts causing the patient great physical discomfort. *B*, The nipple was transplanted on either breast, and two weeks later the required amount of breast tissue was resected.



A.

B.

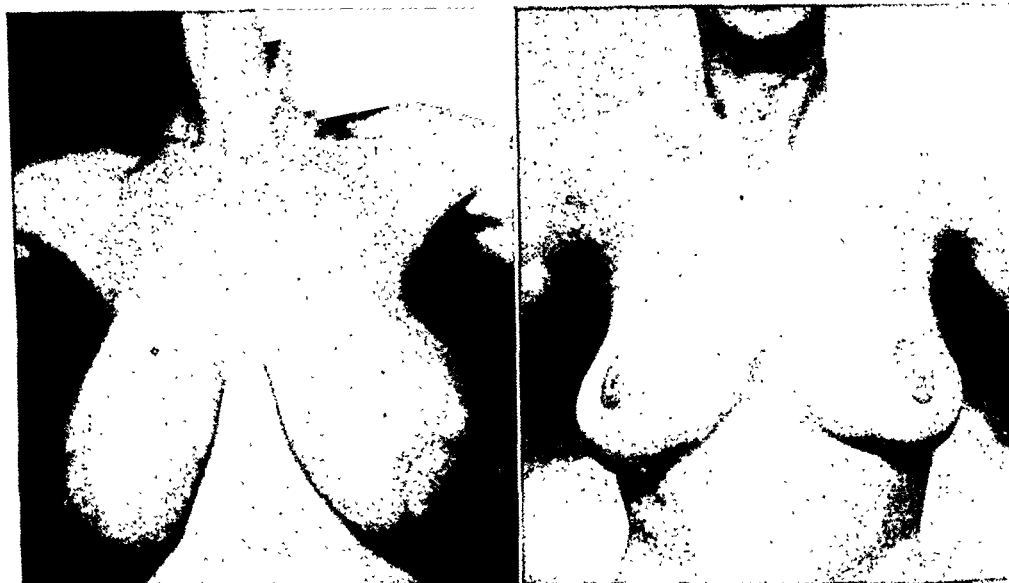
Fig. 13.—*Two-Stage Mastopexy With Nipple Transplant. . . . Author's Modification After Thorek:* A, Pendulous nonfunctional breasts in a younger girl. B, Photographs taken four months afterward, demonstrating the surgical result.



A.

B.

Fig. 14.—*Two-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* A, The nipple with its areola attached to the partially denuded breast is transferred to its new position. The upper pole is fixed to pectoral fascia with silk. A fortnight afterward, the required amount of breast tissue is resected by excising triangular wedges. The skin flaps are cut, adjusted, then approximated with silk to form an inverted T. B, Photographs taken three months following the second stage operation.



A.

B.

Fig. 15.—*Two-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* A, The weight of the breasts caused the patient great physical discomfort. These breasts were functionless and ideal for a two-stage operation. B, Two and one-half months following surgery.



A.

B.

Fig. 16.—*Two-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* A, Markedly hypertrophied, asymmetrical breasts requiring reconstruction. B, Six weeks following surgery.

perpendicularly upward to the new nipple site. The skin of the breast is undermined in a thick flap and the plane of cleavage located. Trauma must be avoided; gentleness is primary or a loss of skin flap may occur. Oftentimes, the skin may be peeled away from the tissue with the aid of a sponge, while in some cases careful spreading with a scissors in the line of cleavage will gain the required result.

The breast, entirely denuded of skin with its nipple and areola attached, is pushed up to the desired position on the chest. This allows the surgeon an opportunity to evaluate the amount and area of breast tissue to be removed. Either two or three triangular wedges of tissue extending down to the pectoral fascia are resected. The areas are closed by approximating the walls with silk sutures.

Following satisfactory reconstruction of the breast proper, three heavy silk sutures are taken through the pectoral fascia over the second rib, carried through the upper poles of the breast, and the latter is fixed to its new position. Sulfanilamide crystals are sprinkled throughout the whole area.

A circular button of skin previously marked to serve as the new location for the areola and nipple is now removed. The skin flaps from either side are brought around the breast, meeting in the center where the excess is excised (Fig. 4 E). The subcutaneous tissue is approximated and the skin closed with interrupted silk sutures. A Penrose drain is inserted beneath the flaps through either corner of the lower incision.

The opposite breast is similarly reconstructed. Care is taken to create symmetry and similarity between the two breasts. If the decision is to place one nipple slightly lateral, then the other must be placed in a comparable location. It requires more time and effort to reconstruct two nearly identical breasts, both of desirable shape, position, and symmetry. However, a pleasing end result always compensates the surgeon for his thoroughness.

The dressing is applied: parresine mesh impregnated with petroleum jelly over the wound edges, gauze flats over the breasts, and moderate pressure with a stockinet bandage.

Some of the silk sutures are removed at the end of the sixth day, the remainder on the eighth day. The brassière is adjusted and used for support as the swelling subsides.

Two-Stage Mastopexy With Nipple Transplant

Oftentimes in a markedly enlarged breast, it may be the surgeon's opinion that a two-stage operation with nipple transplant is the method of choice. Thorek⁹ was the first to describe this operation. Modification of his original method will depend upon the individual surgeon.^{1, 10}

Author's Modification.—The circular area which is to be the recipient bed for the nipple transplant is carefully measured and marked with a 3 per cent gentian violet solution. Following this circle, an incision is made through part of the derma and the skin is dissected free leaving a bed for the reception of the nipple and its areola. All bleeding is controlled.

An incision is made around the areola following a previously marked circle, and the structure is dissected free almost as a full-thickness graft. The nipple with its areola is transferred to its recipient bed and sewed in place with interrupted fine silk sutures.

A similar procedure is followed on the opposite breast. A suitable pressure dressing is applied. The sutures are removed about the tenth day when pressure is reapplied and the area is treated similar to a full-thickness graft.

Second Stage.—After two weeks, the secondary procedure is carried out under general anesthesia. An incision is made from the center of the nipple downward; another is run along the undersurface of the breast (Fig. 4 A). Two thick skin flaps are created similar to the method in the one-stage mastopexy. The required amount of breast tissue is resected in the form of triangular wedges. The walls are approximated with silk and sulfanilamide crystals sprinkled over the area.

The skin flaps are cut and approximated in the shape of an inverted T. This allows for the reconstruction of a more shapely breast with the desired anteroposterior dimensions and conical symmetry. The inframammary scar is virtually hidden by the lower pole of the breast, while the handle of the inverted T shaped scar is not too noticeable.

Two-Stage Mastopexy With Transposition of the Nipple

This operation is applicable to excessively large breasts that have hypertrophied and retained an abundance of fatty tissue. An attempt to reconstruct a breast of this type to a normal size in a one-stage operation will usually result in necrosis of the nipple and a bizarre breast contour. Or it may result in a breast that is only slightly smaller with its pendulousness retained but now added to it, surgical scars.

Author's Modification.—Under general anesthesia an incision is made around the areola retaining the desired amount for transfer. From the center of the upper edge of this circle, an incision is carried perpendicularly upward to within one-half inch of the new nipple site. From the lower center of the circle an incision is carried perpendicularly downward to the inframammary line. Another incision, some four inches long, is carried around the inframammary line forming an inverted T. Either one or two triangular wedges of breast tissue are taken from the upper pole and the walls approximated. The skin over the breast is undermined in a thick flap to an area just below the clavicle. The upper pole of the breast is fixed at three points, with heavy silk sutures, to the pectoral fascia over the second rib.

A circular area of skin having been previously marked as the new nipple site is excised, and the nipple with its areola is carefully sewed into its new residence. Sulfanilamide crystals are sprinkled into the wound. The excess amount of skin from the apron flap is removed with a semicircular incision and the edge sewed to the lower skin flap with interrupted silk sutures. A Penrose drain is inserted high into either corner of the wound,

A similar procedure is performed on the opposite side. Moderate pressure and support are applied with a stockinet bandage.

Second Stage. A fortnight later, the nipple having gained sufficient circulatory support in its new residence, the patient is again submitted to surgery.

The previous line of incision along the inframammary region is opened and from its center an incision is made upward to the center edge of the nipple forming an inverted T. Two thick triangular flaps are then created by undermining, thus exposing the right and left poles of the breast. Depending upon the amount of breast tissue to be removed, either two or three triangular-shaped wedges are taken, and if necessary a semicircular section is removed along the inframammary region. The walls are approximated with silk.

The required amount of skin is removed both from the center of either flap and from its inferior portion. The wound edges are approximated subcutaneously and the skin is sewed with interrupted silk sutures. A Penrose drain is placed in either angle of the wound.

A similar procedure is repeated on the opposite side with care and effort expended to create both breasts of equal size and shape and at the same time conical with the required anteroposterior dimensions. Suitable pressure dressing is applied.

SUMMARY

Enlarged and pendulous breasts usually may be reconstructed in a one-stage operation. This procedure allows for both breasts to be virtually identical and to retain their physiologic function. The author's modification of this method permits the breasts to be reconstructed to the desired size, shape, and contour and results in smaller postoperative scars.

In some cases, depending upon the judgment of the surgeon, a two-stage operation may be required. Either transposition or transplantation of the nipple may be employed at his discretion.

REFERENCES

1. Adams, W. M.: Free Transplantation of the Nipples and Areolae, *SURGERY* 15: 186-195, 1944.
2. Barnes, H. O.: The Correction of Pendulous Breasts, *Am. J. Surg.* 10: 80-83, 1930.
3. Berson, M. I.: Mammoplasty for Pendulous Hypertrophied Breasts, *M. Rec.* 153: 89-92, 1941.
4. Fisher, G. A., et. al.: Massive Breast Hypertrophy in Adolescence, *The Western Journal of Surgery, Obstetrics and Gynecology* 51: 349-55, 1943.
5. Gillies, Harold, and McIndoe, A. H.: The Technique of Mammoplasty in Conditions of Hypertrophy of the Breast, *Surg., Gynec. & Obst.* 68: 661, 1939.
6. Maliniac, J. W.: Breast Deformities, *Am. J. Surg.* 39: 54-61, 1938.
7. May, Hans: Reconstruction of Breast Deformities, *Surg., Gynec. & Obst.* 5: 77, 1943.
8. Thorek, Max: *Plastic Surgery of the Breast and Abdominal Wall*, Springfield, Ill., 1942, Charles C Thomas, Publisher.
9. Thorek, Max: Possibilities in Reconstruction of Human Form, *New York Medical Journal and Record* 116: 572, 1922.
10. Updegraff, Howard L.: Reconstruction of the Breast, *California & West. Med.* 46: 28-31, 1937.

TREATMENT OF PUBERTAL BILATERAL GYNECOMASTIA

REPORT OF A CASE

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INTRODUCTION

SINCE diffuse enlargement of the breast in the male unassociated with tumors of the genital system occurs with some frequency and has been a source of much debate, we were led to study in some detail a case of bilateral hyertrophy in a 16-year-old boy.

On a histologic basis a number of workers^{1, 2} have classified enlargements unassociated with malignant tumors into two classes, true gynecomastia and pseudogynecomastia. The first shows proliferation of ducts and periductal connective tissue, while the second shows normal male breast tissue and is presumed to be due to localized fat deposits or to overgrowth of fibrous connective tissue following injury (chronic fibrous mastitis). Any relation of these to endocrine disorders has been questioned.

In favor of endocrine participation is the fact that many of the enlargements occur when the male is at the age of puberty or soon thereafter, without a history of trauma. In many cases some phases of puberty have been delayed. And in a number of instances considerable reduction in the size of the breast has followed the prolonged administration of androgens.^{3, 4}

The group of cases described by Klinefelter, Reifenstein, and Albright⁵ showed bilateral enlargement of the breasts associated with small testes, aspermatogenesis, and little growth of facial hair. There was a normal growth of pubic hair and external genitals. The excretion of 17-ketosteroids was normal to definitely subnormal. In the two cases tested, the estrogen secretion was normal. They report no benefit from administration of androgens.

The case to be described is that of a 16-year-old young man with bilateral gynecomastia developing at puberty. In many respects he resembled the cases described by Klinefelter and his associates. The quantitative changes in volume of the breasts and the 17-ketosteroid excretion were followed during a period of intensive therapy with testosterone.

This work was aided by a grant from the Graduate Research Fund, University of Minnesota.

Received for publication Aug. 28, 1944.

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CASE HISTORY

Past History.—A 16-year-old, unmarried, white, male student had noticed gradual increase in the size of both breasts for two years, associated with breast pain. Except for scarlet fever at the age of 10, his general health had been excellent. Past history was noncontributory. Development had been normal, voice changing at the age of 14 years. He had experienced erections, nocturnal emissions, and sexual intercourse with ejaculations.

Examination.—The patient was a tall, asthenic individual. He measured 69 inches in height and weighed 143 pounds. Increased adiposity was noticed about the mammae and trochanteric areas. There was no beard, although fine dark hair was present on the upper lip. The axillary hair was sparse, the pubic hair was abundant but with the female escutcheon. There was virtually no hair on the trunk or extremities. The carrying angle was increased. The skin was soft, smooth, somewhat dry, with a minimum of oiliness. The facial appearance was boyish, demeanor unassuming; the voice was low in pitch and masculine. The thyroid cartilage was not prominent.

The breasts were symmetrically enlarged, with the consistency, size, and configuration of a well-developed adolescent female. The nipples were moderately retracted with a dark areolar pigmentation. No discharge was obtained from either nipple. The chest measured 35 inches around the nipple line.

He complained of a sense of fatigue and narcolepsy. The external genitals were well developed. The seminal vesicles were not palpable and the prostate was very small.

Laboratory Data.—The Kahn and Wassermann tests were negative. Studies of the urine and blood were within normal limits. Blood cholesterol was 158 mg. per 100 c.c., the basal metabolic rate was -7 and -2 per cent, bleeding time (ear) $3\frac{1}{2}$ minutes, clotting time (ear) $2\frac{1}{2}$ minutes. Plasma proteins were normal, prothrombin time 19.4 minutes (control 19.2). Serum phosphatase was: acid 9.9, alkaline 10.2 mg. Hippuric acid and cephalin-cholesterol tests were within the normal limits. Sperm counts on two occasions were found to be 2,200,000 per c.c. Of the sperm present, only 25 per cent showed motility and normal morphology.

Roentgen Reports.—The following roentgen report was submitted:

Aug. 7, 1942, Skull: The skull appeared entirely normal except for some sclerosis of the mastoids. The sella turcica appeared normal. Conclusions: Negative skull and sella turcica; sclerotic mastoid.

Aug. 25, 1942, Pneumo-adrenogram: There was a good insufflation of air about the left kidney and in the left adrenal space. On the right side, the insufflation was less satisfactory as the air was injected somewhat lower down. The left adrenal was clearly made out, but I believe it was within normal limits. Conclusion: Probably negative adrenal.

Sept. 8, 1942, Pathology: There was no evidence of pathology in the lungs, mediastinum, diaphragm, or pleura. The heart appeared normal. Conclusions: negative.

Sept. 18, 1942, Examination: Simple examination of the urinary tract showed no evidence of abnormality. The epiphyses for the crest of the ilia would indicate some slight advance in ossification although this is probably of the upper limits for the age of 16. The epiphyses of the spine were within normal limits in their degree of development.

Course of Therapy.—October, 1942, six injections of 1 c.c. of antuitrin compound were given at weekly intervals without any apparent effect in arresting the mammary development.

Two series of twenty-four hour collections of urine were analyzed for 17-ketosteroids and estrogens; one before any treatment and one during ineffective gonado-

*Report of Dr. Leo Rigler, roentgenologist at the University Hospitals.

trophic administration (Table I). The average excretion of 17-ketosteroids was 5.8 mg. in twenty-four hours, a value below that which we have obtained in normal young men (9 to 20 mg. in 24 hours). The estrogen level (9 to 26 I.U.), on the other hand, was well within the normal range.

TABLE I
ESTROGEN ACID 17-KETOSTEROID EXCRETION

SAMPLE NO.	COLLEC- TION PERIOD (IN HR.)	DATE	URINE VOL. (IN C.C.)	ESTROGENS I.U. PER 24 HR.	17-KETOS- TEROIDS MG. PER 24 HR.
1	24	8/13/42	1770	7.8	6.1
2	24	8/14/42	1080		4.9
3	24	8/15/42	1950	9.0	6.4
4	24	8/16/42	1420		
5	24	10/11/42	1680	21.0	6.2
6	12	10/14/42	765		5.8
7	12	10/15/42	725	11.0	7.4
8	12	1/14/43	650	15.0	7.0
9	12	1/13/43	680		7.1
10	12	1/15/43	900		4.8?
11	12	3/17/43	530	>11	10.8?
12	?	3/18/43	1140		17.5
13	?	3/19/43	610		11.8
14	9	4/14/43	360		5.8
15	13	4/15/43	260	10.0	4.7
16	13	4/16/43	650		8.0
17	24	4/21/43	950		1.5
18	24	4/23/43	580		3.1

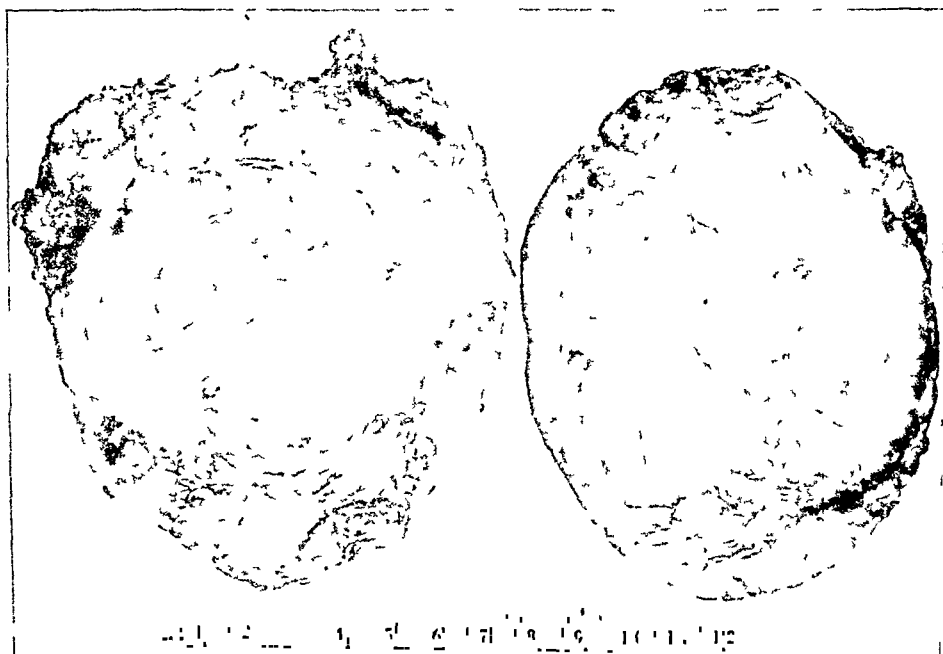
Since there was some evidence of a decrease in the 17-ketosteroids, to which the naturally excreted androgens belong, an intensive course of androgen therapy was tried. Intramuscular injections of 25 mg. testosterone propionate* were administered daily for fifty days.

The following changes were observed during the intensive course of replacement therapy. The prostate increased in size, but remained small, and the seminal vesicles became palpable. There was no increase in libido or in nocturnal emissions. Sense of well-being and energy improved, although the narcolepsy increased but later improved. The previous unassuming attitude changed to one which was more aggressive. Facies became more mature. Acne did not appear on the face but was noticed on the shoulders and arms. The increase in sebaceous secretion and ruddiness developed in the face. The voice became rough and deeper pitched. There was an easily discernible increase in the size of the skeletal muscles, especially about the shoulder girdle and an increase in height of 1½ inches. The patient noticed increased strength and improvement in psychologic outlook.

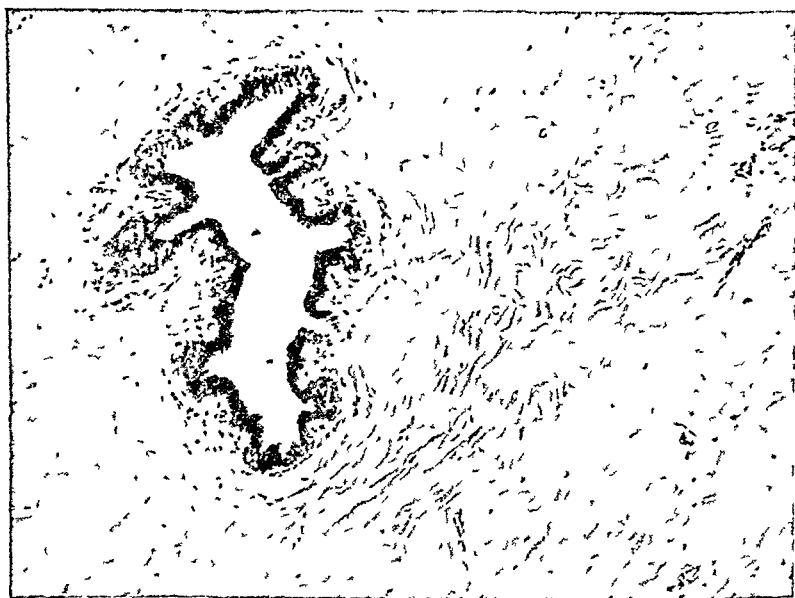
The effectiveness of the therapy is indicated by the increase in the excretion of 17-ketosteroids as shown in Table I. There was no evidence of drug toxicity. The breasts appeared to decrease slowly in size during this treatment. This was

*The testosterone propionate was furnished by Ciba, Pharmaceutical Products Inc., Summit, N. J.

beard was delayed, the testes were small, and prostate and seminal vesicles were not well developed. This was associated with a low excretion of 17-ketosteroids. It would appear that in this case there was some deficiency in androgens.



A.



B.

Fig. 3—Appearance of breast tissue removed at operation. A, Gross appearance of masses removed from both breasts. B, Typical section through breast tissue.

Unlike the results reported by the Boston workers, we did obtain some reduction in mammary size during treatment with testosterone. This may have been due to more intense treatment on our part; again it may have been due to our ability to identify partial changes by the methods used. It is improbable that the change was coincidental since duplicate casts some time apart during the preliminary control period did not show such variation.

This change was apparently due to a direct effect on the gland, since there was no general loss of water or protein from the body; instead, the total weight increased. Since the glands were largely composed of connective tissue with occasional ducts and alveoli, it is probable that the shrinkage was in the ducts, and that there was a lower limit below which testosterone would have had no further effect. Perhaps if androgen therapy had continued for a sufficient time and had been checked by volume measurements, a similar decrease would have been found in the cases of Klinefelter and his associates. While surgical removal still remains the treatment of choice, the endocrine involvement in this syndrome should not be forgotten.

SUMMARY

1. A case of bilateral gynecomastia developing at puberty is reported in a 16-year-old boy. It was associated with little beard development and some evidence of improper or subnormal testicular function. The 17-ketosteroid output was low.

2. Administration of testosterone daily for three weeks decreased the volume of the breasts by about 50 per cent, while the general body weight increased. The excretion of 17-ketosteroids was also increased. The change in the gland appeared to be decreasing with time, however, and surgical removal was resorted to.

3. The histologic picture was one of chronic fibrous mastitis. The case appears to have been another of the syndrome described by Klinefelter, Reifenstein, and Albright.⁵

4. While a considerable reduction in the size of the breasts can be produced in these cases by intensive treatment with testosterone, the result is not sufficiently cosmetic, probably because of the increased residual connective tissue, to justify its use. The surgical approach is to be preferred. Androgen therapy can be used subsequently if it seems indicated.

REFERENCES

1. Lewin, M. L.: Gynecomastia, *J. Clin. Endocrinol.* 1: 511-514, 1941.
2. Maliniac, J. W.: Breast Hypertrophy in the Male, *J. Clin. Endocrinol.* 3: 364-366, 1943.
3. Wernicke, H. O.: Gynecomastia, *SURGERY* 5: 217-225, 1939.
4. Hoffman, W. J.: Hormone Therapy of Male Breast Hypertrophy, *Am. J. Cancer* 36: 247-251, 1939.
5. Klinefelter, H. F., Reifenstein, E. C., and Albright, F.: Syndrome characterized by Gynecomastia, Aspermatogenesis Without A-Leydigism, and Increased Excretion of Follicle-Stimulating Hormone, *J. Clin. Endocrinol.* 2: 615-627, 1942.

EFFECTS OF ENVIRONMENTAL TEMPERATURE ON THE TRAUMATIC SHOCK PRODUCED BY ISCHEMIC COMPRESSION OF THE EXTREMITIES

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CRUSHING injuries of the extremities may lead either to shock or to a delayed disturbance of renal function known as the crush syndrome. In a study¹ of an ischemic form of crushing injury in dogs, ten out of eleven of our experimental animals, studied at ordinary laboratory temperatures, died within a few hours after release of the compression with a shocklike course characterized by an initial rapid decline of mean arterial pressure followed by a slower progressive fall of pressure ending in death. Since the one survival occurred on a day when the temperature in the laboratory was unusually low we entered upon an investigation of the effects of environmental temperature upon the shock produced by this type of trauma, the results of which are presented in this paper.

METHODS

In this study both hind legs of dogs were crushed and rendered ischemic by applying a tightly wound spiral of rubber tubing from the ankle to the groin. The dogs were placed in cages and the rubber tubes removed after six hours. Administration of morphine, 4 mg. per kilogram, plus sodium pentobarbital, 20 mg. per kilogram, prevented pain during the period of compression but allowed the animals to be well awakened within one or two hours after release of the tubes. A few dogs received small additional injections of morphine during the period of compression.

A first group of sixteen control dogs was studied at ordinary laboratory temperatures which varied from 19.8° to 27.0° C. during the winter months and from 24.0° to 27.9° during May. A second group of fourteen dogs was kept in a cool environment in a room, maintained at 9° to 14° C., from the start of compression until twenty to twenty-four hours after removal of the rubber tubes. The dogs were then returned to the laboratory. Feeding was omitted on the morning of the experiment and water, available until the dogs were anesthetized, was withheld for the next thirty hours. Hematocrit readings were made of venipuncture blood. Rectal, intramuscular, and subcutaneous temperatures were recorded continuously.²

Read at the meeting of the American Medical Association, June 14, 1944, Section on Pathology and Physiology.

Supported by a grant from The Commonwealth Fund.

Received for publication, Sept. 7, 1944.

*On leave of absence from the Department of Physiology, Laval University School of Medicine. Aided by a grant from the Province of Quebec, Canada.

The amount of edema in each traumatized leg was computed from the difference in the volume of water displaced when the leg was immersed in a tall narrow-mouthed cylindrical vessel before compression and again after death, or, in those dogs that survived, twenty-four hours after release of compression.

RESULTS

The dogs in both groups of experiments were, at the moment of release of compression, in varying stages of anesthesia from moderately deep to very light and a few in each group were attempting to sit up. Within a few minutes after release of the rubber tubes all the dogs became stuporous. Those kept in the laboratory usually remained semicomatose until death. In marked contrast to these, the dogs in a cool environment were found sitting up or standing within two to three hours after release of the compression.

The durations of survival of all dogs studied in this investigation are presented in Table I. This table clearly demonstrates that a cool environment during the period of compression and for a reasonable length of time afterward increases the viability of dogs subjected to this form of trauma.

The temperatures of the subcutaneous tissues and of the muscle of the compressed extremities declined rapidly after application of the rubber tubes and were approximately at the environmental temperature when the rubber tubes were removed. As a result, the temperature of the compressed tissues was considerably lower throughout the period of compression in the dogs kept in the refrigerated room than in those kept in the laboratory. The rectal temperatures of the control dogs were strikingly different from those kept in a cool environment. The former were between 35.3° and 41° C. until release of compression and then steadily rose, reaching temperatures of 39.0° to 43.1° C. at the time of death. The rectal temperatures of the latter ranged from 32.5° to 40° C. during compression, and in the case of all but one of the dogs that survived, remained relatively stable between 35° and 38.9° C. The rectal temperatures of five of the dogs in the refrigerated room dropped relatively rapidly to 28° to 34° C. during the night. These dogs were then warmed, but only one survived. The courses of the rectal temperature of a representative group of dogs are plotted in Fig. 1.

The dogs studied in May were weighed at the start of the experiment and again after death, or, if they survived, at twenty-four hours after release of the compression. Table I shows that the dogs kept in a cool environment and those in the laboratory lost approximately the same amount of weight, expressed in grams per kilogram of body weight. It should be noted, however, that the rate of loss of body weight was considerably more rapid in the latter group since their survival was much shorter than the thirty-hour interval between the initial and final weighing of the former group.

TABLE I

RECTAL TEMPERATURE ° C.																										
NUMBER OF DOGS	DIED IN - HOURS AFTER RELEASE OF LIMB COMPRESSION		ENVIRONMENTAL TEMPERATURE ° C.				DURING PERIOD OF LIMB COMPRESSION				AT RELEASE OF LIMB COMPRESSION				SIX HOURS AFTER RELEASE OF COMPRESSION OR AT DEATH IF SURVIVED LESS THAN 6 HOURS				24 HOURS AFTER RELEASE OF COMPRESSION OR AT DEATH IF SURVIVED 6 TO 24 HOURS							
							RANGE		AV.		RANGE		AV.		RANGE		AV.		RANGE		AV.		RANGE		AV.	
A1	1	Survived				19.8	19.8	35.6-39	37.3	38.0	39.2	37.0	37.0													
A2	10	0.8-18	5.2	7.3		23-27	24.6	36.8-41.0	39.5	39.2-41.0	40.0	39.0	39.0*													
B1	3	Survived				9-12	10.5	35.0-38.5	36.2	37.5-38.5	38.0	36.2	36.3													
B2	4	22-48	35	14.2		9-12	10.5	35.5-40.0	37.3	35.5-40.0	37.1	31.3	29.6													
C1	0	Survived				-	-	-	-	-	-	-	-													
C2	5	4-19	8.2	5.9		24.0-27.9	26.5	35.3-40.3	38.1	37.0-40.0	38.7	40.0	41.1†													
D1	6	Survived				10.3-13.0	12.3	32.5-38.0	35.8	33.0-39.0	36.9	36.9	37.9													
D2	1	9.5	9.5	-		11.3	11.3	36.0-38.0	37.0	37.5	37.5	31.0	26.0													

	WEIGHT LOSS IN GM. PER KG.		LOCAL EDEMA IN COMPRESSED LEGS						AUTOPSY OF LEGS, NUMBER OF DOGS IN EACH CATEGORY						STUDIED IN	
			MEASURED		ESTIMATED MAXIMUM											
RANGE	AV.	RANGE	AV.	RANGE	AV.	σ	AV.	ERROR	0	+	++	+++	++++	{ Dec. to Feb. (controls)		
A1	-	-	-	17†	-	30†	13.7	-	8.5	-	5	-	1		0	{ Dec. to Feb. (cool environment)
A2	-	-	-	16‡	-	29§	-	-	7.8	-	2	-	0		0	
B1	-	-	-	16‡	-	29§	-	-	7.8	-	2	-	0	0	{ May (controls)	
B2	-	-	-	16‡	-	29§	-	-	7.8	-	2	-	0	0		{ May (cool environment)
C1	-	-	-	34	-	48	5.9	-	5.8	-	0	-	0	3		
C2	29.5-59.0	39.9	26-41	36	-	39	8.6	-	2.2	-	0	-	0	0	{ May (cool environment)	
D1	26.5-47.6	33.7	22-46	25	-	39	-	-	6.5	-	0	-	0	0		{ May (cool environment)
D2	31.5	31.5	25	25	-	39	-	-	6.5	-	0	-	0	0		

*One dog survived longer than six hours.

†Two dogs survived longer than six hours.

‡Edema measured on four dogs of this group.

§Edema measured on one dog of this group.

Survival, environmental, and rectal temperatures, weight loss, and local edema in anesthetized dogs traumatized by six hours of ischemic compression of their hind legs.

Av. = average, σ = standard deviation of individual determinations about the average, computed as:

$$\sigma = \sqrt{\frac{\sum(X - \bar{X})^2}{N-1}}, \text{ where } \bar{X} = \text{individual determination on each dog, } X = \text{average of these determinations, and } N = \text{number of dogs.}$$

The measured local edema in the compressed legs is expressed in ml. per kgrm. of body weight. It is the sum of the edema in the two traumatized legs. In determining the volume of edema each hind leg was immersed three or more times during the control period before compression of the legs, and again after death, or in the case of a few of the dogs that survived, twenty-four hours after release of compression. The difference between the means of the control and post-mortem immersions divided by the weight of the dog gave the measured edema of the leg. Control experiments indicated that an edematous leg shrinks approximately 5 ml. per kilogram of body weight when the animal dies. These studies also showed that approximately 10 per cent should be added to allow for edema of proximal tissues, not detected by the immersion method. Addition of these two corrections to the measured edema yields the volume which is tabulated as the estimated maximum edema.

Av. Error. This is an expression for the probable error of the estimated maximum edema. It was computed as follows: For each measurement of limb volume several immersions were made. The standard deviation of the difference between the control and the post-mortem volume for an extremity was computed as

$$\sigma I = \sqrt{\frac{\sum(\bar{X}_c - \bar{X}_e)^2 + (\bar{X}_{pm} - \bar{X}_{pm})^2}{N_c - 1 + N_{pm} - 1}}$$

where \bar{X}_c are the individual measurements at each immersion, \bar{X}_e is the mean of these measurements during the control period, \bar{X}_{pm} and \bar{X}_{pm} are the corresponding measurements after death, and N_c and N_{pm} are the number of immersions, respectively. Using σ_e , the standard deviation for the change in volume of a leg with death,¹ = 2.0, then the total standard deviation for the estimated maximum edema in both legs in a dog is:

$$\Sigma\sigma = \frac{2}{\Sigma\sigma} \sigma_e + \frac{\sigma I(n)}{\Sigma\sigma} + \frac{\sigma I(1)}{\Sigma\sigma}$$

In the table the column labeled Av. Error is the average of the $\Sigma\sigma$ for all the dogs in the group.

In the columns labeled Autopsy of Legs, + = just detectable moistness, ++ = obvious edema, +++ = marked gelatinous edema of the soft tissues, ++++ = marked gelatinous edema of the soft tissues with marked swelling and paleness of the compressed muscle.

Fig. 1.

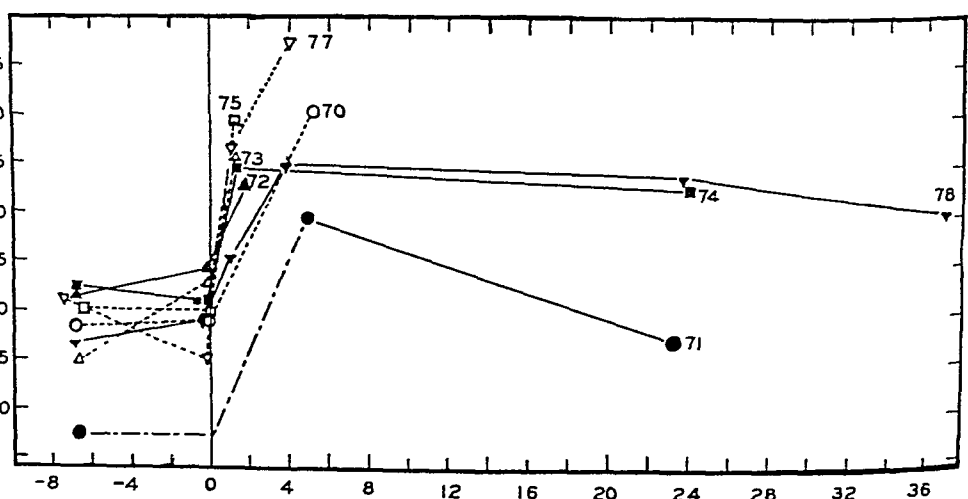
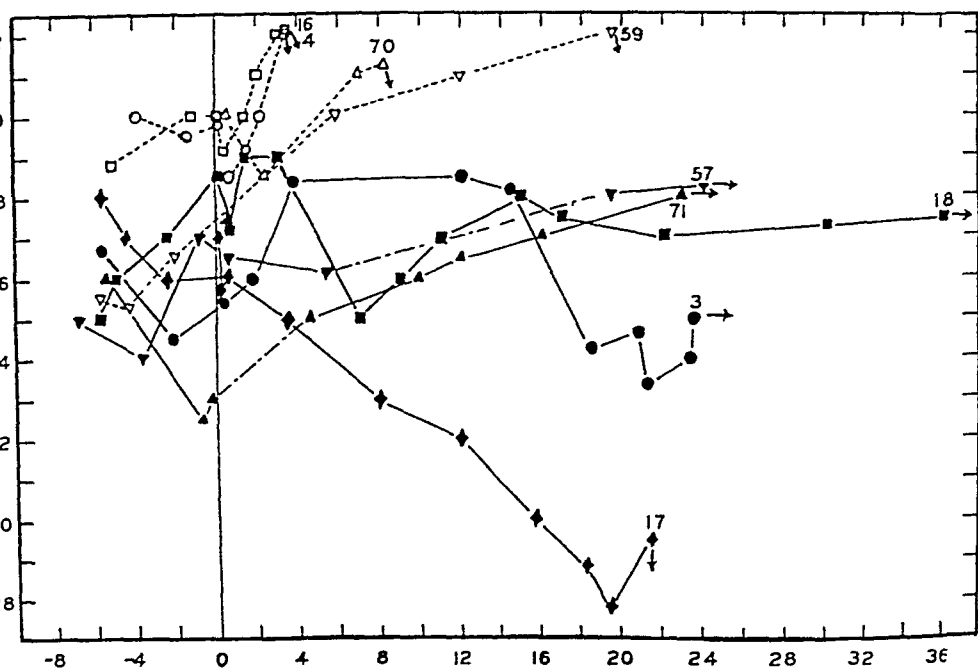


Fig. 2.

Fig. 1.—Plots of the rectal temperatures during and after application of ischemic compression to the hind legs of dogs anesthetized with morphine and sodium pentobarbital. Ordinate scale shows rectal temperature in degrees centigrade. Abscissal scale gives time in hours; zero time is moment of release of compression of hind extremities. Solid symbols and solid or dot-dash lines represent dogs kept in a cool environment; hollow symbols and dotted lines, dogs kept in the laboratory at ordinary temperatures. Corresponding symbols (for example, solid and hollow triangles) refer to animals studied simultaneously. Arrows with downward tip indicate the moment of death; arrows with tip pointing to right indicate complete survival. Dot-dash line signifies that temperature was not recorded continuously during the indicated interval.

Fig. 2.—Plots of the successive changes in hematocrit readings during and after trauma, as indicated in Fig. 1. Ordinate scale shows cell volume per cent of blood volume. Abscissal scale, symbols, and numbers have the same significance as in Fig. 1.

The hematocrit readings of the dogs kept in the laboratory rose somewhat more rapidly and reached higher levels than those of the dogs kept in a cool environment. These differences are illustrated in Fig. 2.

Post-mortem examinations were performed on all dogs that died. The findings in the traumatized legs are summarized in Table I. In addition to the varying degrees of edema, small hemorrhages were occasionally seen in the muscle or soft tissue. The traumatized muscles, particularly of the dogs studied in May, showed many regions of pallor. It has not been determined whether the pallor is due to loss of myoglobin or to separation of the muscle fibers by edema. Myoglobin has, however, been demonstrated in the urine of three dogs of another series of experiments which showed similar changes in the muscle. Occasional mild hyperemia of the lungs, omentum, and subcutaneous tissue of the thorax was seen in the dogs dying in the winter months, but no significant differences were noted between those dying at ordinary laboratory temperatures and those dying at low environmental temperatures. In contrast to these, all six of the dogs that died during May showed marked hyperemia of the cortex and papillae of the kidneys, and moderate to marked hyperemia of the subcutaneous tissue of the thorax, omentum, and duodenal mucosa. Free blood was found in the lumen of the duodenum of only one of the dogs kept in the laboratory and in the one which died in a cool environment.

Of the six dogs which survived in May, five were killed, two, five, nine, eleven and thirteen days after release of compression. Except for small superficial cutaneous ulcers on the traumatized legs of the last three dogs, all of the dogs were in good condition. Four of the five had lost 25 to 134 grams per kilogram of body weight, the larger losses occurring in the latter dogs. Essentially no residual edema was found on the eleventh or thirteenth days of survival, although small areas of pallor were observed in the crushed muscles. In the dogs killed on the second and fifth days the edema was as great as when measured twenty-four hours after release of compression. Except for moderate hyperemia of the duodenal mucosa, all other tissues were normal to gross examination.

Complete microscopic examinations* were made on two of the dogs which survived and were killed two and five days after release of the compression. In both dogs mild passive hyperemia and slight fatty metamorphosis were seen in the central zones of the liver. The epithelium of the tubules of the kidneys was narrowed and coarsely granular, and the proximal and distal tubules and the broad loop of Henle showed irregularly distributed foci of fatty degeneration. There was much acidophilic precipitate in the tubular lumen of the dog sacrificed after two days. The lumen of the glands of the duodenal mucosa contained what was apparently inspissated, deteriorated blood. In one dog the spleen showed diffuse slight fibrosis and the deposit of a great deal

*These studies were made by Dr. Howard T. Karsner, professor of Pathology and director of the Institute of Pathology.

of pigment of dark golden yellow and of light orange-yellow shades. The compressed muscle of the thighs showed various degrees of necrosis and hyaline degeneration. The cytoplasm was scanty and the nuclei of the muscle fibers were large and vesicular, each containing a nucleolus. Granulation tissue was present in the degenerating muscle and there was proliferation of large mononuclear cells, evidently of the sarcolemma. Fat stains were negative.

Table I shows that no significant difference was found between the *measured edema* of the dogs kept in the laboratory and those kept in a cool environment. When allowance is made, however, for certain technical errors of the immersion method,¹ the resulting volume, recorded as the *estimated maximum edema* in Table I, is found to be slightly greater in the former than in the latter.

Eight additional dogs were subjected to certain modifications of these experimental procedures during the winter months. The traumatized legs of two dogs were cooled by placing ice about them during the period of compression, while their bodies remained at room temperatures of 26° to 28° C. Both died in five and one-half hours. The traumatized legs of three dogs were placed in a chamber in which air, cooled to 7° to 14° C., was circulated while their bodies remained at room temperatures of 22° to 26° C. Two survived and one died at six hours. Concurrently with the latter dogs, the bodies of three dogs were placed in the cooling chamber while their legs remained at room temperature. One survived, the others died at six and eight and one-half hours.

During May, two dogs were kept at laboratory temperatures of 25.5° to 28.2° C. during the period of compression. Immediately after release of compression the dogs were placed in cages at environmental temperatures of 12° to 14° C. One was returned to the laboratory at twenty-four hours and died nine hours later; the other remained in the cool environment until it died at thirty hours.

DISCUSSION

The effects of warming or cooling traumatized extremities have been studied by Allen,^{3, 4} Duncanson and Blalock,⁵ and Blalock.⁶ These authors are all in agreement that cooling the traumatized extremities especially during the period of trauma lessens the severity of the shock and prolongs the survival. Blalock and Mason,⁷ and more recently Antos⁸ have studied the effects of a cool environment on the shock which follows a period of hypotension produced by bleeding. Both obtained a longer survival but no decrease in the per cent of fatality. Elman, Cox, Lischer, and Mueller⁹ concluded that rats with severe body burns survived best at environmental temperatures near ordinary room temperature, and Wakim and Gatch¹⁰ arrived at similar conclusions for rats, guinea pigs, and dogs traumatized by intestinal stripping. Unfortunately, little data is available regarding the rectal temperatures of the latter two groups of animals subjected to different environmental temperatures after trauma. Since the environmental temperature in their

experiments was the temperature of a platform on which the animals were placed, it is probable that the body temperatures were depressed below normal at environmental temperatures below normal body temperatures.

Our experiments demonstrate that controlled cooling of the body and legs during and after release of compression is an effective procedure in preventing this form of shock. Furthermore, there seems to be good evidence that whether the traumatized legs are cooled or not, placing the body in a cool environment increases the viability of anesthetized dogs subjected to ischemic compression trauma.

Four mechanisms require consideration in explaining the improved viability of our dogs exposed to a cool environment.

1. The lower temperature of the compressed tissues may have slowed metabolic action and tissue disintegration and, as a result, less toxic material may have entered the blood stream upon restoration of the circulation. Proof of this hypothesis must await evidence that blood returning from these traumatized extremities has a toxic action upon the body.

2. In addition to this, cooling might have reduced the vascular damage and thereby decreased the loss of plasma into the traumatized tissues. The somewhat smaller estimated maximum edema of the dogs in a cool environment and the slightly greater viability of the dogs whose extremities alone were cooled offer support for this hypothesis. However, the equally good results in those experiments in which the body only was cooled, or in which the dogs were placed in a cool environment only after release of compression, demonstrate that this mechanism is not the sole factor in explaining the better survival of our dogs placed in a cool environment.

3. It is commonly considered that a cool environment may aid by reinforcing compensatory cutaneous vasoconstriction. Since we wished to use minimal anesthesia and to allow our animals complete freedom of movement, it was not possible to study this factor in the present experiments.

4. As indicated by our records of mean arterial pressure, there occurs a marked depression of the circulation immediately after release of compression. Accompanying this, there is in all probability a diminution in the blood supply to vital tissues. In the presence of an elevated or even normal body temperature there is undoubtedly a discrepancy between the blood supply and the metabolic needs of these tissues during this period of circulatory depression. According to the proponents of the vicious cycle theory, this will lead in turn to further depression of the circulation and ultimately to death. On the other hand, the depressed circulation may be able to meet the demands of the tissues when their metabolism is reduced by lowering the body temperature and a fatal outcome may thereby be delayed or even obviated. This hypothesis is strongly supported by the observation that without exception in our experiments those dogs which survived maintained rectal temperatures

at or below 39° C. during the critical twenty-four hours after release of compression, whereas, all the dogs which died while kept at ordinary laboratory temperatures had rectal temperatures above this level during all or most of the time from release of compression to death. According to the observations of one of us (H. D. G.) and co-workers,² the normal range of rectal temperatures for dogs is 37° to 39° C. with an average of 38.5° C.

SUMMARY

Fifteen of sixteen anesthetized dogs subjected to a six-hour period of ischemic compression of their hind legs and kept at ordinary laboratory temperatures of 20° to 28° C. died in an average of 6.4 hours after release of the compression. Fourteen dogs were similarly traumatized but placed in a cool environment of 9° to 14° C. during and for twenty-four hours after the compression. With one exception all lived longer than twenty hours and nine survived indefinitely after release of compression. It is concluded that in these experiments the beneficial effect of the cool environment is due in part to diminishing the damage to the traumatized tissues during the period of compression, and in part to decreasing the metabolic demands upon the circulation by moderate lowering of the body temperature during the critical first twenty-four hours after release of compression. The evidence suggests, however, that rectal temperatures below 34° C. are not well tolerated. Facilitation of cutaneous vasoconstriction may also play a part, but evidence for this mechanism has not been obtained. Dogs studied in the spring reacted to this form of trauma with the production of more edema at the site of the compression and with more systemic hyperemia than did dogs studied in the winter.

REFERENCES

1. Green, H. D., Antos, R. J., Dworkin, R. M., and Bergeron, G. A.: Ischemic Compression Shock, With an Analysis of the Local Fluid Loss, *Am. J. Physiol.* 142: 494-507, 1944.
2. Green, H. D., Nickerson, N. D., Lewis, R. N., and Brofman, B. L.: Consecutive Changes in Cutaneous Blood Flow, Temperature, Metabolism and Hematocrit Readings During Prolonged Anesthesia With Morphine and Barbitol, *Am. J. Physiol.* 140: 177-189, 1943.
3. Allen, F. M.: Surgical Considerations of Temperature in Ligated Limbs, *Am. J. Surg.* 45: 459-464, 1939.
4. Allen, F. M.: Theory and Therapy of Shock; Reduced Temperatures in Shock Treatment, *Am. J. Surg.* 60: 335-348, 1943.
5. Duncan, G. W., and Blalock, A.: Shock Produced by Crush Injury, Effects of Administration of Plasma and Local Applications of Cold, *Arch. Surg.* 45: 183-194, 1942.
6. Blalock, A.: A Comparison of the Effects of Local Application of Heat and Cold in Prevention and Treatment of Shock, *SURGERY* 11: 356-359, 1942.
7. Blalock, A., and Mason, M. F.: A Comparison of the Effects of Heat and Those of Cold in Prevention and Treatment of Shock, *Arch. Surg.* 42: 1054-1059, 1941.
8. Antos, R. J.: Influence of Hypothermia and Hyperthermia on Survival Time of Dogs in Hemorrhagic Shock, *Proc. Soc. Exper. Biol. & Med.* (In press.)
9. Elman, R., Cox, W. M., Lischer, C., and Mueller, A. J.: Mortality in Severe Experimental Burns as Affected by Environmental Temperature, *Proc. Soc. Exper. Biol. & Med.* 51: 350-351, 1942.
10. Wakim, K. G., and Gatch, W. D.: Effect of External Temperature on Shock, *J. A. M. A.* 121: 903-907, 1943.

ARTERIAL SPASM SECONDARY TO LIGATION AND RETROGRADE INJECTION OF THE SAPHENOUS VEIN

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LIGATION of the internal saphenous vein at present is an accepted and commonly practiced procedure. The essential prerequisite for its execution has been the satisfactory demonstration of an adequate deep venous circulation by means of the various functional tests, the chief of which are those introduced by Trendelenburg, Perthes, Ochsner, and Mahorner. Accurate preliminary determination of the degree of arterial sufficiency to the part, however, has been commonly neglected. The experiences sustained in Cases 1 and 2 have suggested the study described in this report.

CASE REPORTS

CASE 1.—M. P., a white man, aged 54 years, came to us with varicose veins of the right leg and thigh. The symptoms were those of fatigue and discomfort along the inner aspect of the thigh after prolonged standing. There were no complaints suggestive of an impaired arterial circulation, such as intermittent claudication, coldness of the feet, disturbance of sensation, or fatigue on walking. The remainder of the present and past history was negative except for excessive smoking for many years, and a worrisome temperament.

Physical examination revealed a well-preserved and a fairly well-developed patient. The blood pressure was 145/90 and a routine urine analysis was negative. There were no remarkable physical findings except for the varicosities of the right lower extremity. The right leg and thigh presented a moderate-sized dilatation of the internal saphenous vein with tortuous branching dilatations over the inner upper two-thirds of the leg. Incompetency of the valves of the saphenous vein were readily demonstrated by means of the Trendelenburg test. Adequacy of the deep venous circulation was satisfactorily proved by both the Perthes, and the Ochsner and Mahorner tests. The arterial circulation in the foot seemed adequate, the dorsalis pedis and the posterior tibial pulses being readily palpable and of fair volume. The color and the temperature of the foot were normal and the Silbert passive flexion test failed to produce any abnormal degree of plantar ischemia. No oscillometric determinations had been made, this not having been part of the routine preoperative examination of that time.

Oct. 14, 1941, under local anesthesia, division and ligation of the right saphenous vein at the saphenofemoral junction were performed. Five cubic centimeters of 2 per cent sodium ricinoleate were injected into the distal segment at the time of operation. The immediate postoperative reaction and the convalescence were uneventful. In the following weeks sclerosing injections of 5 per cent sodium morrhuate were given to occlude the residual patent veins.

Oct. 28, 1941, following the injection of 1 c.c. of 5 per cent sodium morrhuate, the patient went into a state of profound allergic shock characterized by vomiting, cyanosis, absent blood pressure, extremely faint pulse, blood tinged expectoration, and diffuse urticaria. With appropriate treatment he recovered after one and one-half hours.

Nov. 21, 1941, the patient returned with the complaint of intermittent claudication occurring after walking a short distance. Examination at this time disclosed an absence of a palpable pulsation in the dorsalis pedis, posterior tibial, and popliteal arteries of the right leg. The right femoral pulsation in Scarpa's triangle could be obtained. The corresponding pulsations of the left leg were readily elicited.

Arterial occlusion of the vessels of the right lower extremity had evidently occurred. It was difficult to decide whether such a complication was the result of the ligation and retrograde injection of a sclerosing agent, or whether it was precipitated by the acute allergic shock that occurred at the later date.

CASE 2.—S. G., a white woman, aged 44 years, on examination was found to show moderately extensive varicosities of both legs with incompetent internal saphenous veins on both sides. The only complaints were the unsightliness and a sense of heaviness in both legs. Her health was good in all other respects and the antecedent history was irrelevant. Physical examination was negative except for the varicose veins as just described. The urine was negative. The feet were of normal color and exhibited good surface temperatures. Both dorsalis pedis and posterior tibial pulses were readily palpable and of good volume. Oscillometric determination taken at the lower third of the leg was 2 for each side. A bilateral saphenous ligation with retrograde injection of 5 c.c. of 2 per cent sodium ricinoleate on each side was done under local anesthesia in the customary fashion. The patient was made immediately ambulatory. Three days later she presented herself complaining of coldness of both feet. Examination disclosed a faint weak dorsalis pedis pulse on both sides with pallor and coldness of both feet. Oscillometric readings at the same level showed an excursion of $\frac{1}{2}$. These findings persisted for two months, when the patient was lost trace of.

Accumulating clinical and experimental evidence shows that occlusion, chemical irritation, or bacterial inflammation of a segment of a large vein will cause ipsilateral reflex arterial spasm with diminution in the peripheral pulse volume. DeBakey, Burch, and Ochsner have shown that ligation of the proximal portion of the femoral vein in dogs resulted in marked diminution (52.5%) in the volume of the pulsations in the foot, as determined with the aid of an accurately recording plethysmograph. Preliminary resection of the corresponding paravertebral sympathetic ganglia or injection of novocain into the perivascular tissues of the isolated venous segment failed to influence the resultant decrease in volume of the arterial pulsations. This fall in pulse volume appears to have been due to the resultant increase of venous back pressure which was transmitted through the capillary bed against the arterial pressure. Subsequent injection of the chemical irritant into the lumen of this vein or into its perivascular tissues also produced a further marked decrease (51.6%) in the volume of the peripheral pulsations. In the latter case however, either preliminary resection of the paravertebral sympathetic ganglia or perivenous novocain infiltration into the segment of vein neutralized this action.

Reflex arterial spasm, secondary to severe thrombophlebitis, has become an accepted clinical entity. In extreme instances the ischemia resulting from such arterial spasm may simulate an arterial embolus or, where the spasm persists, may precipitate actual gangrene. Isolated

case reports of such occurrences have appeared increasingly in the literature in the past ten years. The syndrome evidently had been misinterpreted up to that time. The mechanism producing the arterial constriction is a sympathetic reflex caused by impulses originating in the involved venous segment. Paravertebral infiltration of the corresponding sympathetic ganglia with procaine will interrupt such reflex action. Similarly, perivenous infiltration of the venous segment with procaine prior to the injection of the chemical irritant also prevents the reflex spasm. The spasm resulting from the localized process in the vein, whether traumatic, bacterial, or chemical may occur in both arteries and veins. Injection of a potent sclerosing solution into a varicose vein results in a dramatically visible and palpable venospasm within one or two minutes. It is not uncommon for a dilated internal saphenous trunk one inch in diameter to shrink to the size of a lead pencil following the injection of 2 to 5 c.c. of a potent sclerosing agent. Traumatic venospasm is at times observed where repeated unsuccessful attempts at vein puncture have been made. This contractile power appears to be retained by dilated varicose veins, despite their atony, dilatation, and loss of elasticity.

Prompted by the experience in the two cases quoted, the following studies were entered into for the purpose of determining the effect that the clinical ligation of the saphenous vein together with the retrograde injection of a sclerosing agent had upon the arterial circulation.

PROCEDURE

The data were obtained from fifty consecutive cases in which saphenous vein ligations and retrograde injections were performed. The accepted prerequisites for saphenous vein ligation are:

1. A dilated internal saphenous trunk with incompetent valves
2. Patency of the deep veins as judged by the clinical appearance of the leg, together with the accepted functional tests.
3. General good health, as evidenced by the history, cardiac sufficiency, satisfactory blood pressure, and normal urine analysis
4. Adequate arterial circulation to the part, as determined by the history, the presence of palpable dorsalis pedis and posterior tibial pulsations, and a satisfactory appearance and surface temperature of the part
5. The absence of acute phlebitis, acute inflammation, or grossly infected ulceration
6. An oscillometric determination within normal limits

The patients were ambulatory prior to the operation, receiving a preliminary oral dose of $1\frac{1}{2}$ gr. of sodium pentobarbital. The blood pressure (brachial) was taken preoperatively and postoperatively in twenty patients. Oscillometric determinations were made in the lower third of the leg at constricting pressures of 160, 140, and 120 mm. of mercury.

Simultaneous oscillometric readings were taken pre- and postoperatively in the forearm in ten patients and in the leg upon which operation was not done in ten other patients.

The skin and tissues over and about the saphenofemoral junction were infiltrated with 1 per cent novocain free of adrenalin. The proximal portion of the saphenous trunk was exposed by a two-inch horizontal incision made directly over the fossa ovalis. The segment of the vein was isolated from its sheath for a distance of three inches below the saphenofemoral junction. It was clamped, divided, and resected for a distance of two inches. The proximal and distal ends were transfixed and ligated. From 3 to 5 c.c. of 2 per cent sodium ricinoleate, in accordance with the size of the vein, were injected into the distal segment.

In ten patients oscillometric readings were taken immediately following division of the vein and again directly after injection. In all patients, oscillometric readings were taken at the completion of the operation or approximately within fifteen minutes after injection of the sclerosing solution. Readings were taken again one hour after the injection. Ten patients were hospitalized and readings made over a twenty-four hour period. All patients were made immediately ambulatory, so as to diminish the hazard of postoperative emboli. A Collin oscillometer was used for all determinations. The accepted normal oscillation was found to vary from two to six.

RESULTS

In evaluating the effects of surgical venous trauma and chemically produced phlebitis any appreciable deviation in the oscillometric reading from the preoperative normal was considered evidence of arterial spasm. No untoward reactions followed the procedure. There was no evidence of novocain shock or sensitivity to the sclerosing agent in any of the patients. In most instances there was a burning or cramplike sensation in the leg shortly after the retrograde injection of the sodium ricinoleate, which persisted for varying lengths of time. In many patients this would be followed by the subjective and objective signs of a chemical phlebitis in the veins of the thigh and leg, to a varying degree. The arterial spasm seemed to be roughly proportionate to the degree of immediate postoperative discomfort, that is, the more the burning and cramp, the greater the drop in the oscillometric reading. In most instances the maximum arterial spasm was detected about thirty minutes postoperatively.

1. There was no appreciable change in the postoperative brachial blood pressure as compared with the preoperative reading in any of the twenty patients so studied. This would tend to show that any resultant arterial spasm in the leg produced no recognizable effect upon the systemic blood pressure.

2. Oscillometric readings taken in the upper extremity directly following those taken in the involved legs showed no change from the preoperative determinations. Likewise, readings taken in the opposite

leg, when that extremity was not treated by ligation and retrograde injection, showed no change from the readings obtained preoperatively. This would tend to corroborate the clinical and experimental work of Leriche, Ochsner and DeBakey, and DeBakey, Burch, and Ochsner, in that the arterial spasm secondary to a phlebitic process is reflex and is confined solely to the homologous extremity.

3. In five patients no change in oscillometric readings occurred up to ninety minutes postoperative. In one instance the readings were higher by 1 to 2 points. No certain explanation can be given for these latter inconsistencies. The chemical phlebitis may not have been sufficiently severe to produce a reflex arterial spasm. The spasm might have been transitory, having possibly occurred in between the readings, which were taken every fifteen to thirty minutes.

4. In ten patients, readings were taken immediately after division and ligation of the vein, but before the sclerosing solution was injected into the distal segment. No change was noted in any of these. This would tend to show that trauma upon a small segment of the vein was not sufficient to produce a reflex arterial spasm of sufficient degree to be detected by our method of study. DeBakey, Burch, and Ochsner, however, were able to produce experimentally increased intra-arterial pressure, as determined by the plethysmograph, by exclusion without division of a small segment of the femoral vein.

5. In forty-five patients there were definite postoperative falls in the oscillometric readings. Since the preoperative oscillometric determinations varied from 2 to 6, it was thought best to interpret the degree of arterial spasm in terms of percentage deviation from normal rather than the actual change in scale reading of the oscillation itself. For example, a patient with a preoperative reading of 6 and a postoperative reading of 2 would have a percentage change in oscillometric reading of 66 per cent. This showed a mean change of 54 per cent, the individual minimum being 20 per cent and the individual maximum 75 per cent.

The arterial spasm appeared from five to thirty minutes after the retrograde injection, reached its peak from thirty to sixty minutes after such injection, and usually returned to normal in four to six hours. Ten of these forty-five patients were observed over a period of twenty-four hours. Eight of these exhibited normal readings at the end of this time, whereas two still showed a persistence of arterial spasm at the end of the twenty-four hours.

INTERPRETATION

In the use of the oscillogram the occurrence and degree of arterial spasm has been gauged by an indirect method rather than by direct determinations on the arteries themselves. The difficulties of direct measurements of intra-arterial pressures in human beings are obvious. Oscillometric determinations have been universally accepted as a satisfactory means of determining the adequacy of the circulation in the larger arteries, even though the patency of the small arteries and

arterioles cannot be detected in this way. It was felt that this method of detecting arterial spasm was adequate for these studies, and one that could roughly lend itself to quantitative clinical application.

This study has been a clinical evaluation of the effect upon the arterial circulation by the presently accepted combination procedure of saphenous ligation and retrograde injection of a sclerosing agent. Arterial spasm followed the division and retrograde sclerosis of the saphenous vein. It did not appear directly after the division and ligation of the vein. Since it did appear at varying intervals after the irritative effects of the sclerosing agent, and since it was roughly proportional to the degree of reaction, one is prone to attribute the resultant spasm to the induced chemical phlebitis. No attempt had been made to determine the occurrence of delayed arterial spasm in a series of cases where just division and ligation of the vein had been performed. It is noted by us, and by others, that ligation and division of the saphenous vein alone would be followed by collapse, occlusion, and thrombosis of the vein distal to the level of the ligation. Such effect might also induce a reflex arterial spasm and may be worthy of investigation.

CONCLUSIONS

1. The results of this study confirm experimental findings and clinical observations that phlebitis, either chemical, infectious, or traumatic, may produce reflex arterial spasm.

2. The widely practiced procedure of saphenous ligation and retrograde injection of a sclerosing agent is commonly followed by a varying degree of arterial spasm in the homologous extremity.

3. Such resultant arterial spasm may precipitate a further increase of arterial circulatory insufficiency in instances where an impaired arterial circulation already exists.

4. These observations emphasize the necessity for the determination of the degree of arterial sufficiency to the part when division and retrograde injection of the saphenous vein are anticipated. Precipitation of an impending or partial arterial occlusion into a more complete form may result from the arterial spasm induced by this procedure.

REFERENCES

1. Ochsner, Alton, and DeBakey, Michael: Therapy of Phlebothrombosis and Thrombophlebitis, *Arch. Surg.* 40: 208-231, 1940.
2. DeBakey, M., Burch, G. E., and Ochsner, A.: Effect of Chemical Irritation of Venous Segment on Peripheral Pulse Volume, *Proc. Soc. Exper. Biol. & Med.* 41: 585, 1930.
3. Ochsner, A., and DeBakey, M.: Thrombophlebitis; The Role of Vasospasm in the Production of the Clinical Manifestations, *J. A. M. A.* 114: 117, 1940.
4. Andier, M.: Thrombosis Veineux aigues simulant l'embolie arterielle des membres (Acute Venous Thrombosis Simulating Arterial Embolism), *Paris méd.* 100: 384-389, 1936.
5. Leriche, R.: Considerations sur le traitement chirurgical de la phlébite du membre inférieur et de ses séquelles éloignées, *J. Internat. de Chir.* 3: 585, 1938.
6. Bergendal, S.: Gangrene of the Foot After Venous Thrombosis, *Acta chir. Scandinav.* 68: 528, 1931.

VASCULAR INSUFFICIENCY OF THE LOWER EXTREMITY DUE TO OSTEOMA OF THE FEMUR

CASE REPORT

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IN THIS paper is reported a patient with typical intermittent claudication relieved by removal of an osteoma of the femur.

Impairment of the blood supply of the lower extremity is a relatively common occurrence. In the great majority of cases the diminution in blood flow is due to intrinsic lesions in the walls of the arteries and veins. Nové-Josserand* has reported a case in which the femoral artery was traumatized against an underlying femoral exostosis, producing a false aneurysm which caused impairment of the arterial supply of the lower leg. Perusal of the literature has failed to reveal a case in which vascular obstruction was caused by a benign tumor of the femur.

CASE REPORT

A. G., a 48-year-old white man, was admitted to the Orthopedic Service of Barnes Hospital, July 18, 1944, and was discharged July 27, 1944. Sixteen years previous to admission the patient had noted a hard, painless swelling on the medial aspect of the left thigh just above the knee. This swelling gradually increased to the size of a hen's egg over a period of six years, following which it had ceased to enlarge. Except for the presence of the tumor itself, the lesion had been asymptomatic until four years prior to admission when the patient began to notice that the left leg tired more easily than the right. This gradually increased in severity until seven months previous to admission when he developed intermittent claudication of the left leg. He was unable to walk more than a city block without experiencing severe pain in the left calf. The pain necessitated his resting, which immediately brought relief. The pain was described as a severe ache—"My calf felt like it was going to burst out." The patient volunteered that the pain and walking were always accompanied by a great distention of the veins of the lower extremity. The pain so incapacitated the patient that he was forced to cease working two months previous to admission to the hospital. At that time he developed severe pain whenever he attempted to walk more than ten steps.

On admission to the hospital the physical and laboratory examinations were essentially normal, with the exception of those relating to the local lesion. There was a hard, fixed, nontender mass 5 by 6 cm. in diameter located on the medial supracondylar line 10 cm. from the distal end of the left femur. The left foot and lower extremity were cooler than the right, and the left dorsalis pedis and posterior tibial arteries could not be palpated. There were no trophic changes in the nails or skin. When the patient was in the supine position there was definite engorgement of the veins of the left lower leg. There were a few small varicosities around the malleoli. The skin in this region showed a dusky cyanotic discoloration. The cyanosis and the venous distention were increased in the dependent position. On elevation of the extremity the veins emptied slowly and the foot became slightly pallid. When the patient walked a few steps there was a great increase in the engorgement of the superficial veins and in the cyanosis of the lower leg. The tumor did not encroach up-

Received for Publication, Oct. 2, 1944.

*Nové-Josserand, M.: *Déchirure de l'artère femorale pars une exostose ostéogénique*, Lyon chir. 24: 234, 1927.

on the long saphenous vein. There was no edema. Radiographs showed a typical osteochondroma of the left femur with some calcification of the femoral artery proximal to the lesion.

Although it was thought that the osteoma and the vascular impairment probably were not related, it was decided that the tumor should be removed. At operation, on exposing the area it was found that the pedicle of the osteoma was located on the medial supracondylar line just distal to the tendinous ring through which pass the

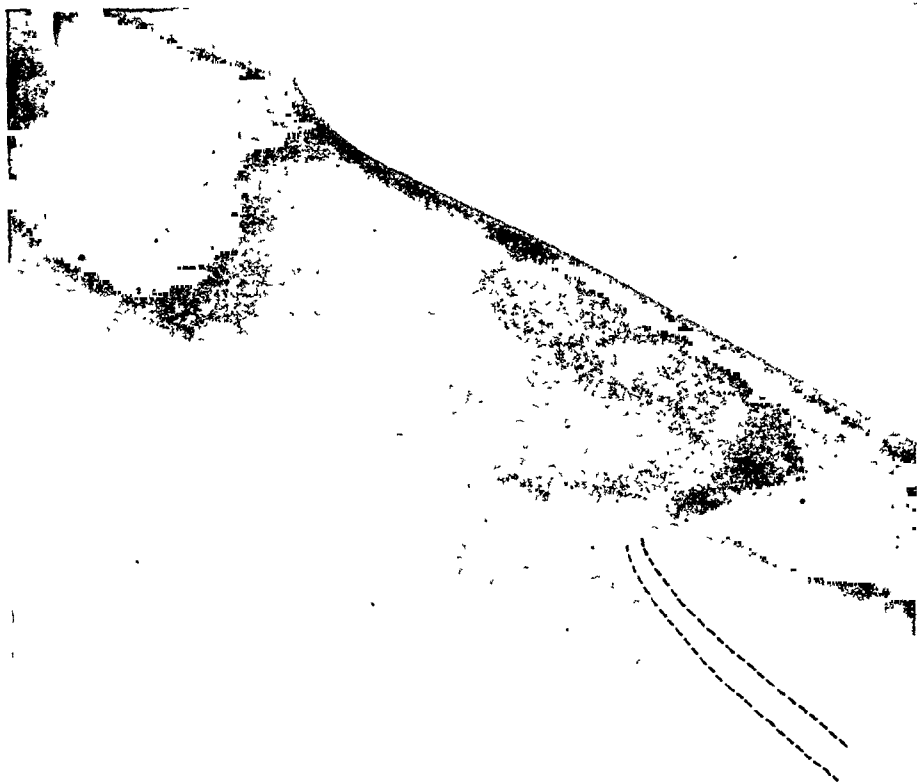


Fig. 1.—Osteoma of the femur which obstructed the femoral artery and vein by compressing them against the tendon of the adductor magnus. The femoral artery, showing calcification in the wall which was clearly visible in the original radiograph, has been delineated in this print.

femoral artery and vein. From its pedicle the tumor had grown superiorly in two walnut-sized masses, one anterior and one posterior to the tendon of the adductor magnus. The Y formed by these two masses compressed the great vessels against the rigid superior margin of the tendinous ring, causing considerable distortion of the vessels and diminution of their lumina. The pulsations of the femoral artery distal to the lesion were present, but markedly diminished in volume. The femoral vein was dilated distal to the obstruction so that the diameter of the distal segment was about twice that of the proximal segment. The osteoma was removed and the wound closed in the routine manner. Pathologic diagnosis of the removed tissue was osteoma of cortical bone.

The patient's postoperative course was uneventful. He was allowed out of bed on the fourth postoperative day and volunteered that for the first time in three years he was able to walk without pain. At the time of discharge no pulsations could be palpated in the left dorsalis pedis or posterior tibial arteries. The skin temperature was higher than it had been before operation, but it was still somewhat lower than that of the right foot. The venous engorgement had almost entirely disappeared. Two months following operation the patient still had some weakness of the left

leg and the extremity felt tired after prolonged exercise. However, he was back at work and there was no recurrence of the intermittent claudication.

COMMENT

This patient's circulatory disturbance apparently was due largely to the partial obstruction of the femoral artery and vein by the osteoma of the femur. The blood flow in the femoral artery was further decreased by the arteriosclerosis in the wall. This process in the vessel wall apparently was caused by the trauma, and constriction of the vessel by the tumor. There were no signs or symptoms of arteriosclerosis in the opposite lower extremity, nor could calcification be seen in the radiograph, or at operation, distal to the lesion. The onset of symptoms did not occur until thirteen years after the appearance of the tumor and seven years after the patient thought it had ceased to grow. This was due to two factors: (1) There was probably continued occult growth of the tumor into the soft tissues of the thigh after subjective enlargement had ceased; and (2) there must have been a gradual increase in the arteriosclerotic process in the arterial walls, both generally and locally, which did not reach a critical point until approximately four years prior to admission, when the patient first developed symptoms. This patient had a gradual occlusion of the femoral artery extending over a period of sixteen years, and yet adequate collateral circulation had failed to develop. This is consistent with the well-known paucity of anastomotic channels around the knee joint. The failure of edema to develop in the presence of markedly increased venous pressure demonstrates very nicely the fact that venous obstruction alone does not cause fluid retention in the tissues.

Although the impairment of venous return was the most striking feature, it seems unlikely that this could have been responsible for the intermittent claudication. The case throws an interesting light on the controversial principle of ligation of the main vein of an extremity when the main artery is occluded. In this case the obstruction of the femoral vein was of a higher degree than that of the femoral artery. Following operation there was clinically a great improvement in the venous return without noticeable change in the arterial inflow. The fact that the patient's circulatory efficiency was obviously greatly increased after the operation by the improvement of venous return is a point against the validity of these principles. Symptomatic relief following operation was dramatic despite the failure of the arterial pulsations in the foot to return to normal. The continued absence of the pulsations was no doubt due to the secondary arteriosclerotic process in the wall of the femoral artery at the site of the tumor.

SUMMARY

A case of intermittent claudication relieved by removal of an osteoma of the femur is presented. The vascular insufficiency was caused by obstruction of the femoral artery and vein by the tumor and by secondary arteriosclerosis of the artery.

PLASTIC CLOSURE OF SKULL DEFECT

CASE REPORT ILLUSTRATING USE OF TANTALUM PLATE AND PEDICLE-TUBE GRAFT

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THE repair of skull defects caused by war injuries to military personnel has become a technical procedure of increasing importance in rehabilitation neurosurgery. Unpublished statistics collected from the existing neurosurgical centers in the Zone of the Interior show that a large proportion of such casualties may be returned to duty. Following the reports of Pudenz¹ and Pudenz and Odom,² tantalum plate has been used extensively for this purpose. Its strength, malleability, and lack of tissue reaction have recommended its clinical trial in an increasing number of cases. The various techniques for the formation and for the fixation of the plate have been described and found adequate in a sufficiently large number of cases.³

Cranioplasty in otherwise normal individuals, that is, individuals without grave neurologic defect and convulsions, may be complicated by residual infection in the scalp, dura, or brain. It may be further complicated by the necessity for staged procedures, and frequently by the problem of extensive scalp loss and its replacement by thin, atrophic scar tissue. Proposed incisions for cranioplasty for war wounds of the head must be placed with due attention to the vascular supply of the involved scalp tissue. The failure to appreciate fully this fundamental surgical principle in a formidable instance of scalp loss and the subsequent course of uncharted surgical therapy are illustrated in Case 1.

CASE REPORT

CASE 1.—Aug. 7, 1943, a 30-year-old soldier received a severe penetrating wound of the left frontal region of the head when struck by a fragment of an 88 mm. shell. The missile produced a compound, comminuted, depressed fracture of the left frontal bone with dural and cerebral laceration. Incomplete débridement was performed forty-eight hours later. The wound became infected, and on Aug. 21, 1943, a secondary débridement was carried out with removal of bone fragments and two foreign bodies. A roentgenogram of the skull taken before this procedure shows the extent and character of the bony defect and the presence of a large shell fragment (Fig. 1). The resulting cerebral fungus subsided, and by September 22, healing was complete. During the first month following injury the patient was described as semistuporous, irrational, and irritable. There was cervical rigidity and weakness of the right upper extremity.

Upon admission to the Ashford General Hospital, Nov. 15, 1943, the neurologic examination showed normal findings. There was a pulsating, locally tender skull defect in the left frontal region, covered by a large, stellate, thin and atrophic scar (Fig. 2). The mobility of the scalp was limited. The extent of the scar, its

Received for publication, Nov. 16, 1944.

location outside the hairline, and the limited mobility of the scalp, appeared to prohibit a massive shift of scalp tissue rostrally, with its attendant secondary scalp defect. A primary pedicle graft was not considered. A decision was reached to carry out a concealed left frontal craniotomy incision well caudal to the scar, to dissect the scalp scar from the underlying cerebral cicatrix, to replace the dura by appropriate means, and to insert the tantalum plate with the hope that the atrophic scalp scar would remain viable. After healing of the proposed dural and skull graft, a secondary plastic revision of the scalp was considered a less dangerous procedure.

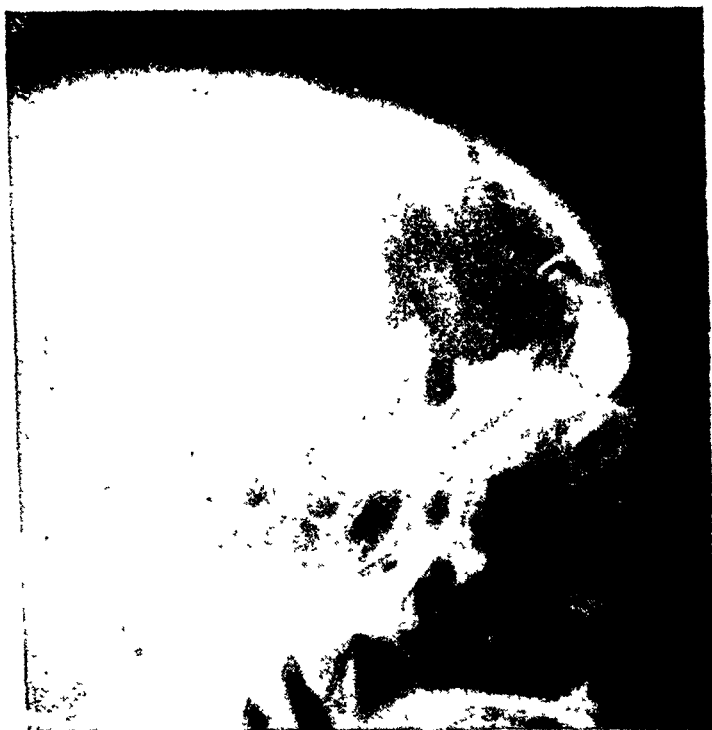


Fig. 1.—X-ray of the skull, showing defect and presence of shell fragment.

Dec. 15, 1943, the scalp flap was reflected. A partially reformed dura was grafted and closed with interrupted sutures of fine silk. A slight leak of subarachnoid fluid persisted between these sutures at the termination of this phase of the repair. A well-fitting, preformed tantalum plate was inserted, and fixation was secured by means of tantalum wire sutures. The scalp flap was closed by the customary two-layer method of suture. At this time the broad scar appeared somewhat cyanotic. (Repair by B. W.)

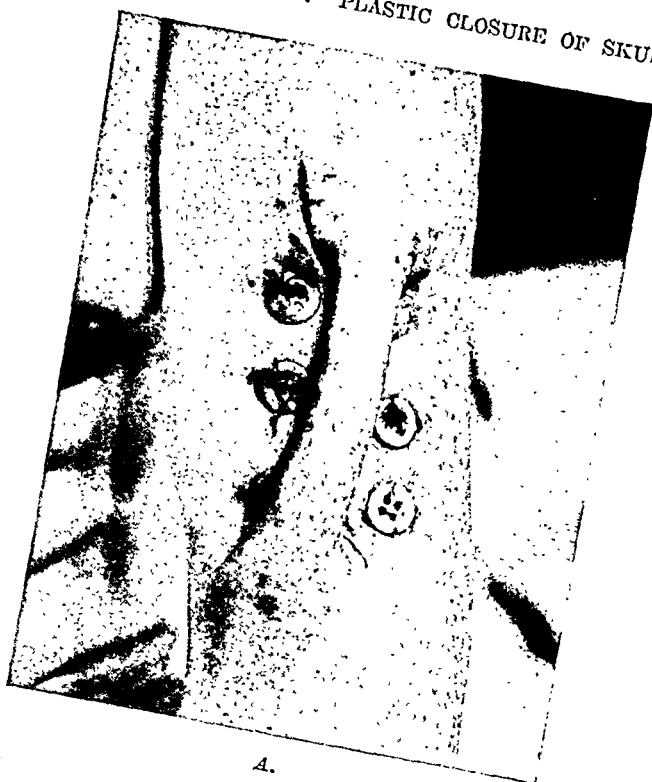
At the end of three days the greater part of the scalp scar had become gangrenous and had sloughed, exposing the underlying tantalum plate (Fig. 3). Culture of an associated purulent discharge showed a hemolytic *Staphylococcus aureus*. Pyogenic invasion of the central nervous system seemed inevitable. Penicillin therapy was started with 30,000 units given intravenously every two hours for eight days; 15,000 units every three hours for three days; and thereafter, because of local irritation, 25,000 units intravenously every three hours for 120 days. Packs saturated with penicillin, 100,000 units per cubic centimeter, were placed in the defect once daily. At no time was there any evidence of localized or generalized infection of the central nervous system.



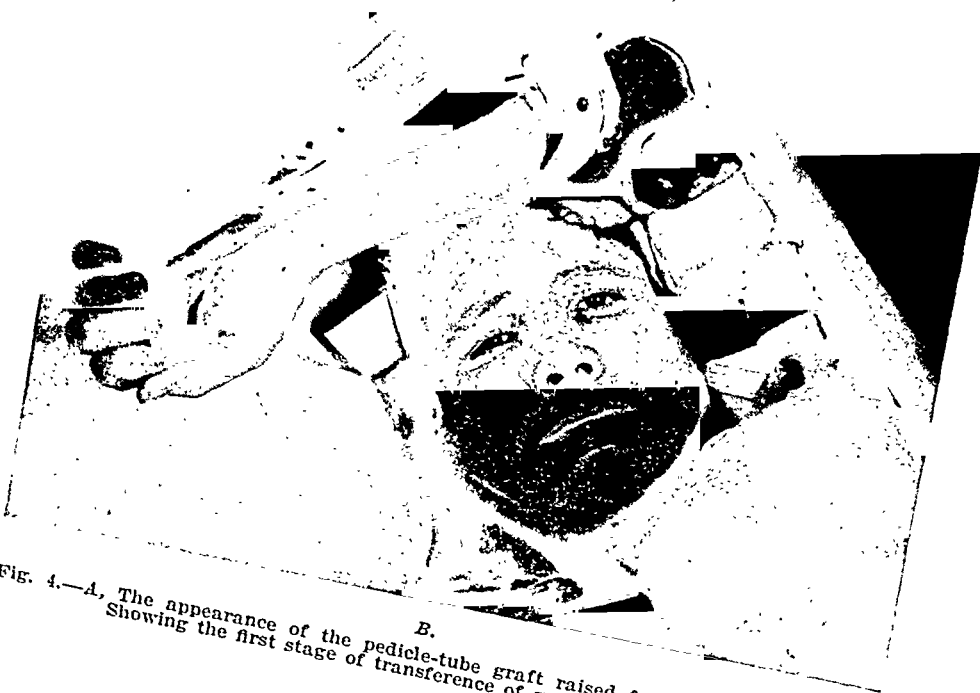
Fig. 2.—The patient before operation, showing thin adherent scar.



Fig. 3.—The patient after operation, showing the exposed tantalum plate after sloughing of the scar.



A.



B.

FIG. 4.—A, The appearance of the pedicle-tube graft raised from the left arm. B, Showing the first stage of transference of graft to scalp defect.



Fig. 5.—The appearance of the graft at the time of the patient's discharge.



Fig. 6.—X-ray of the skull at the time of the patient's discharge, showing tantalum plate.

Jan. 3, 1944, a double pedicle graft was prepared on the anterolateral aspect of the left arm (Fig. 4A). On January 28, the proximal end of the graft was detached, sutured to the edges of the scalp defect, and held in place by a specially devised arm brace (Fig. 4B). On February 17, the remaining pedicle was resected. Complete closure of the scalp defect was carried out April 8, and thereafter the graft healed perfectly (This stage performed by M. H. H.). The appearance of the graft at the time of discharge, June 1, 1944, and the roentgenogram of the skull repair are illustrated (Figs. 5 and 6).

DISCUSSION

The plastic revision of scalp defects has been accomplished in the past by the usual methods of transference of skin from other areas of the body, by secondary relaxing incisions, by undercutting the margins of the scalp defect, by stretching of the scalp, by the use of pedicled flaps of adjacent scalp tissue, and by such elaborate multiple, pedicle graft revisions as described by Tillmanns (Fomon⁴). When the skull is denuded of pericranium, multiple diploic perforations may cause the development of a bed of granulation tissue upon which skin may be transplanted. The problem of replacing extensive scalp scars that are directly adherent to underlying cerebral cicatrices by normal scalp tissue has not received detailed attention. Cutaneous cerebral scars of sufficient magnitude to demand plastic repair may not be uncommon following massive, excavating war wounds of the brain, particularly as a sequel to the regression of a cerebral fungus. Although determined efforts are made by neurosurgeons in active theaters to carry out primary closure without tension with the aid of extensive plastic procedures, the onset of wound infection may vitiate these efforts in a low percentage of cases.⁵⁻⁷

The surgical principle involved in the repair of cutaneous cerebral scars appears to be the prevention of central nervous system infection, no matter what specific method of plastic revision is selected. This necessitates complete closure of the dura by suture or graft, and a closure immune to infection is not technically possible. It follows, therefore, that a potential infection must be prevented by bactericidal or bacteriostatic means. No method of plastic revision of a scar of this character will insure a primary closure of the operative field with the possible exception of a large pedicle graft from adjacent scalp tissue, with its deforming sequel.

The method described in this instance may be a partial solution to this problem. Although the penicillin therapy was undoubtedly overemphasized and unnecessarily prolonged in the light of more recent experience, it appears indisputable that a potential invasive infection may be prevented with penicillin therapy. The sequence of events in this patient has demonstrated the remarkable but characteristic inertness of the element tantalum in tissues. Successful pedicle grafting over a tantalum plate has not been recorded in surgical experience, but there appeared to be no delay in the customary healing time of such grafts. Moreover, the final cosmetic result was satisfactory.

CONCLUSION

Large cutaneous cerebral scars subsequent to extensive war wounds of the head present a problem in plastic revision that has not been solved. A case has been presented in which, through an error in operative technique, a tantalum plate was exposed after gangrene of an overlying, thin, atrophic scalp scar. Invasive infection of the brain was prevented by the use of penicillin while a pedicle graft was prepared and sutured into the resulting scalp defect. Healing of the pedicle graft sutured over the tantalum plate proceeded normally, and satisfactory cosmetic result was obtained. Such a procedure, or a composite variation with primary preparation of the pedicle graft, may offer a solution to this troublesome sequel of head injury.

REFERENCES

1. Pudenz, R. H.: The Repair of Cranial Defects With Tantalum, *J. A. M. A.* 121: 478-481, 1943.
2. Pudenz, R. H., and Odom, G. L.: Meningocerebral Adhesions, *SURGERY* 12: 318-344, 1942.
3. Hemberger, A. J., Whitcomb, B. B., and Woodhall, B.: The Technique of Tantalum Plating of Skull Defects, *J. Neurosurg.* (In press.)
4. Fomon, Samuel: *The Surgery of Injury and Repair*, Baltimore, 1939, Williams & Wilkins Company.
5. Eden, Kenneth: Mobile Neurosurgery in Warfare: Experience in the Eighth Army: Campaign in Cyreniaca, Tripolitania, and Tunisia, *Lancet* 2: 689-691, 1943.
6. Cairns, Hugh: Gunshot Wounds of the Head in the Acute Stage, *Brit. M. J.* 1: 33-37, 1944.
7. Editors: A Review of the Florey and Cairns Report on the Use of Penicillin in War Wounds, *J. Neurosurg.* 1: 201-210, 1944.

PSYCHOSOMATIC FACTORS IN SURGICAL PRACTICE

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THE inability to find an organic basis for a patient's symptoms often poses the most perplexing problem which a surgeon must face. The easiest solution places the patient in the position of being a malingerer, or a neurotic, or in some other category of functional disorders. Physicians who have little insight, or great disinterest, in psychosomatics are inclined to tell the patient reassuringly that there is nothing wrong, and to urge him to "forget it." But try as he may, the patient cannot forget the persisting vertigo, epigastric pain, bloating, and other symptoms, and he consults another doctor about the operation he is sure he needs.

In surgical practice it not infrequently happens that operations are performed for definite organic pathology, which are successful when measured by every accepted standard. Yet the patient complains of the recurrence of the same symptoms, or develops a new group which may not be at all closely related to the previous condition, and is bewildered and resentful when he is told that he is imagining things.

It is well known that emotional disturbances may express themselves through the viscera and other organs, working via the autonomic nervous system to produce symptoms which, as has been well said,¹ "are as little the result of voluntary processes or conscious intent as pulmonary tuberculosis, carcinoma, or heart disease, and equally amenable to the magic of kind words or admonitions." These disturbances may have their roots in such difficulties as marital maladjustment, financial reverses, frustrations and feelings of insecurity or inferiority. The symptoms so produced can be relieved only by treatment of the cause, that is, by straightening out the patient's psychic tangle.

This is not a new concept. The art and science of medical practice are as old as medicine itself. But in this day of precision and mathematical application, we are inclined to overemphasize the science and underestimate the art of practice.

The art of practice deals with the treatment of the patient as a whole, interacting with his particular environment. Extremely significant are the family and friends who comprise the social environment. A more talented sibling, a disgruntled spouse, or a demanding mother-in-law may spark the symptoms which are so distressing. A loafing business partner, an inadequately staffed office, a strike at the plant, or the marriage of an efficient secretary may start rolling a long train of trouble.

The recent medical literature is replete with evidence of the current interest in psychosomatic medicine. A quarterly periodical bearing the title *Psychosomatic Medicine* is a newcomer in the ranks of accepted medical journals. In 1943, a full-grown text, *Psychosomatic Medicine*,² the first of its kind, was published by two well-known teaching clinicians. This is a practical guide which should be of aid to every practitioner. It was followed by another volume, *Psychosomatic Diagnosis*,³ an informative and revealing book. The last revision of Sir William Osler's *Principles and Practice of Medicine*⁴ devoted the first forty-eight pages to psychosomatic interests. For years Alvarez has pleaded with the physician to study psychogenic symptoms instead of brusquely dismissing patients because of their "imaginary" complaints. In the preface to his new book,⁵ an exceedingly valuable treatise, he said:

This is a "different" sort of book—one which deals more with sick unhappy persons than with their diseases, more with symptoms and their meaning than with disease entities, more with the handling of patients than with the giving of medicines, and more with the puzzling, poorly understood and poorly described abdominal discomforts and indigestions than with the well-known organic diseases such as ulcer, cholecystitis and cancer.

Gastroenterology is, of course, the field in which psychosomatic symptoms are most obvious. Even a child learns that too much excitement, like too much candy, makes him sick at his stomach. Nevertheless, psychogenic factors do not, even now, always receive the attention they merit. A recent three-volume study of gastroenterology was criticized because in the consideration of symptomatology the space devoted to psychogenic factors was inadequate from the modern point of view, and not enough attention was paid the relationship of psychosomatic factors to ulcer of the stomach and duodenum.⁶ This criticism, in contrast to the work criticized, indicates the growing recognition of the importance of psychosomatic medicine.

Smith and Rivers⁷ noted the relative unimportance of the diet in the treatment of many ulcers, as shown by the fact that an ulcer may cause severe symptoms which remain unchanged in spite of treatment, until the clearing up of some nervous factor leads to prompt relief. These authors stated that the nervous factor is the dominant causative factor and added: "It is not necessary to psychoanalyze the patient to treat the nervous factors. It is necessary to teach the patient to know himself, his weaknesses and his nervous characteristics and to realize their effect on his ulcer."

Wakefield and Mayo,⁸ in 1938, directed attention to functional disorders of the colon. They said:

The clinical history of a functional disorder of the colon may subjectively reveal the presence of every known symptom which can arise from organic disease of the colon. . . . In eliciting the history, there are certain facts to be ascertained. Organic disease is likely to be ushered in with fever, loss of

weight and perhaps blood in the stool. A functional disorder arises during or following the stress and strain of a social crisis.

These authors described in detail the means of distinguishing between functional and organic disease of the colon, and declared that when careful and complete examination reveals no somatic disease, it is essential to explain to the patient that the symptoms are derived from the autonomic nervous system and are not organic. They concluded:

Surgical treatment of the functional disorders of the colon, as an adjunct to rational therapy, is definitely contraindicated. When operation is performed in the absence of organic disease, it denotes an error in surgical judgment A patient with a functional disorder of the colon may require surgical intervention for other abdominal disease, and fine differential diagnostic judgment is often required in such cases. When it is necessary to operate under these circumstances, it is important to make sure that the patient understands that the proposed operation is not intended to alleviate those abdominal symptoms referable to the functional disease. Surgical advice, therefore, in functional diseases of the colon consists, for the most part, of advice against surgical intervention.

An operation will not cure all of a patient's symptoms unless these are all due to the lesion for which the operation is performed. Brooks⁹ reported that of fourteen consecutive patients operated upon for acute appendicitis, all of whom were observed at operation to have definite acute inflammatory process in the appendix, seven were found on postoperative psychiatric examination to have evidences of anxiety sufficiently grave to be of clinical significance. Two patients operated upon during the same period, who showed no organic change in the appendix, disclosed sufficient evidence to warrant the conclusion that the symptoms and signs which led the surgeon to operate were in reality manifestations of neurosis.

Psychogenic factors in gynecology and obstetrics received extensive editorial comment in *The Journal of the American Medical Association* in 1937. The Journal cited Mayer and stated:¹⁰

Pelvic symptoms are exaggerated more readily than others because many emotional conflicts of women resulting from personal and social restrictions, besides the normal processes of menstruation, defloration and childbirth (all associated with pain and bleeding), center attention on the genital zone and predispose to undue anxiety in connection with local symptoms. The functional cycles are under endocrine control, which is influenced by changes in the sympathetic nervous apparatus, increasing the vulnerability. Acute or chronic psychologic influences, such as fear or frustrated hopes, are associated not only with symptoms but with organic change. Amenorrhea may be a symptom of mental disorders of wide range. Irregular or excessive bleeding may have a psychopathic basis, although here diagnostic curettage should precede the drawing of such a conclusion. Prolonged mental treatment may be needed in dysmenorrhea, in which psychogenic factors are responsible or at least contributory. Certainly expert psychotherapy is indicated before radical operative intervention is attempted.

Seven years later a wartime communication from the Philippines provided striking evidence that amenorrhea may be of emotional origin. Whiteacre and Berrera,¹¹ having observed the women in the Santo Tomas internment camp in Manila, wrote that 14.8 per cent of them suffered from amenorrhea probably due to "severe psychic shock, worry and fear, which, acting through the autonomic nervous system, caused a complete suppression of ovarian function." Food deficiencies, chronic diseases, and other factors, these authors stated, were ruled out.

Psychosomatic symptoms may, of course, direct attention to other than gastric or gynecologic problems. Douglas-Wilson,¹² writing on the somatic manifestations of psychoneurosis, suggested the protean nature of psychogenic functional symptoms. He studied 231 psychoneurotic patients in a military hospital and said:

Nearly all exhibited localized symptoms referred to various organic systems. Cardiovascular disorders such as dyspnea, palpitation and precordial oppression were frequently the most distressing complaints. In other instances the primary symptomatology was referred to the chest, the central nervous system or the digestive and urinary tracts or was constituted by general manifestations, including weakness, nervousness, headache and dizziness.

When after painstaking examination the surgeon discovers that his symptom-ridden patient is free from organic disease, what is he to do? He may by this time have an inkling of the source of emotional conflict or fear. Is it proper for him to try to handle the situation himself? The Journal editorial previously quoted concludes:

Some objections have been raised as to the propriety of the administration of psychotherapy by one who is treating organic ills as well, but in the great majority of cases no ground for such objection exists. Most of these patients do not require formal psychoanalysis but perhaps only simple suggestive treatment, which is best received by their own physician. What is obviously required is the gaining of the patient's complete confidence, an intelligent psychanamnesis, the removal of anxiety where possible, assistance in the acceptance of a reality, instead of a retreat from it, perhaps a change of environment, a building up of the general resistance, local treatment with its suggestive potency, and the judicious use of sedatives, with recourse to a psychoanalyst familiar with these problems when necessary.

The incidence of psychosomatic disease has in itself a bearing on the problem. Rowntree,¹³ discussing Army rejections for neuropsychiatric reasons, said that psychosomatic disease, which in peacetime had a high incidence among white persons but a very low one among Negroes, is increasing in both whites and Negroes. Menninger¹⁴ quoted Surgeon General Norman T. Kirk to the effect that 50 per cent of all civilian patients of all doctors have symptoms derived from emotional disturbances. This author went on to point out that there cannot possibly be enough psychiatrists to handle the problem. Every person practicing medicine, he declared, should be as firmly grounded in psychiatry as in the other basic medical subjects and so be prepared to treat the minor personality disorders.

If Menninger's suggestions with regard to medical education are carried out, the medical schools will provide basic training in psychiatry for the surgeon of the future. The surgeon of today who lacks such training and wishes to equip himself to deal with psychogenic factors as they appear in his practice can do so through postgraduate courses and study of the available literature.

The following case reports illustrate many phases of psychosomatic relationships which the surgeon who wishes to save his patients much suffering, physical and mental, might bear in mind: the great variety of psychogenic symptoms which suggest to patients that they need an operation; the necessity of complete physical, laboratory, and roentgenologic examinations to eliminate or reveal organic disease; the necessity if somatic factors are eliminated of unhurried, careful, and sympathetic investigation of the possibility of psychic disturbances; if these are found, the need of tact and patience in dealing with them; and, finally, the rich reward the surgeon feels in the knowledge that he has avoided an unnecessary operation and has restored to health a patient who might have gone through life a victim of fears, anxieties, and debilitating symptoms.

CASE REPORTS

CASE 1.—Mrs. J. M., a white woman aged 43 years, of English ancestry, complained chiefly of pain in the right lower quadrant, vertigo, pressure in the chest, and bloating. A hysterectomy and appendectomy had been performed six years previously. One physician who had recently examined the patient had suggested an exploratory operation. A second had told her that there was no need for surgical intervention, that she was just imagining her discomfort and should forget about it.

My examination confirmed the absence of organic disease. Questioning elicited the fact that family discord resulted in much tension, with insomnia and a state of anxiety. Apparently the autonomic nervous system had chosen the colon as its seat of expression. The patient was certain that cancer must be developing.

Repeated reassurance of the absence of any organic disease and discussion of the causes of the patient's emotional tensions gradually relieved her fear of malignancy. She has become a healthy, much happier woman and has escaped becoming a victim of multiple operations.

CASE 2.—Mrs. F. L., a white woman aged 44 years, divorced, complained of pain and pressure over the goiter area, epigastrium and lower part of the abdomen, cardiac palpitation and oppression, vertigo, nausea, and irregular menstrual bleeding. In the past several months she had lost twenty pounds.

Seven years before, a cholecystectomy had been performed, and at that time the patient had been apprehensive of malignancy. After an uneventful recovery, however, her fears were allayed. Recently a cousin had died of cancer; her history had been almost identical with that of the patient. Both parents of the patient had died of cancer. During a recent examination elsewhere she had been abruptly informed that she, too, might have a cancer.

The patient looked extremely worried; she was thin and haggard, with tears in her eyes. A fine tremor of the hands was noted when she lighted a cigaret. The pulse rate was 100.

Physical examination showed nothing organically wrong except a uterine fibroid tumor the size of a large orange. The adnexa were not involved. Laboratory tests

gave normal results. The basal metabolic rate was plus 2 per cent and the electrocardiogram normal.

The patient was hospitalized for observation. On the evening of admission she complained of increased dyspnea and cardiac pain. It was apparent that these symptoms had followed receipt of flowers from her divorced husband, whom she still loved and admired. After she had been reassured and her attention directed to the obvious emotional reminder of her former husband, the symptoms subsided.

Each morning time was allotted for a discussion of the patient's emotional fears, and her attention was directed to the lack of symptom relationship between a uterine fibroid tumor and vertigo, nausea, cardiac palpitation and oppression, dyspnea, and goiter distress. One-quarter grain of phenobarbital was administered four times daily. The patient was reminded of her previous cancer phobia and its disappearance.

Each day a small but definite improvement was observed, so that when the necessary operation was performed eight days later the symptoms other than the abdominal pressure had all but disappeared. The resident noted on the chart two days before operation: "The patient feels better than at any time in the past several months." A supracervical hysterectomy was performed and the fibroid tumor, to which but few adhesions were found, removed. The pathologist's diagnosis was "fibroids and fibrosis of the uterus, chronic hyperplastic endometritis." The surgical convalescence was uneventful. The patient lost the appearance of fear, her appetite improved, and she even became cheerful. Her attention was repeatedly directed to the fact that all her symptoms except the pressure in the lower part of the abdomen had vanished before operation and so could not possibly have been related to the tumor.

Comment.—The importance of clearing up the psychosomatic symptoms *before operation* cannot be overemphasized. Clearly, persistence of such symptoms after surgery would have led this patient to believe that a disease process of some sort had been overlooked at operation. Such an occurrence took place in the following case.

CASE 3.—Mrs. R. F., a white woman aged 39 years, of German ancestry, complained of precordial pressure and dyspnea, which were especially severe when she was nervous, and of abdominal pain and fullness, with gas on the stomach varying as to location and intensity. These symptoms had been present for several years, and she was afraid of cancer. The history disclosed that she had always been nervous and sensitive and had feelings of insecurity. Eight months before, a competent surgeon had operated for bilateral hydrosalpinx, removing the fallopian tubes and performing uterine ventral suspension. A letter from this surgeon did not mention nonorganic symptoms continuing postoperatively.

The patient insisted that an exploratory laparotomy be performed. She was convinced that an abdominal cancer had been overlooked.

Complete physical, roentgenologic, and laboratory examinations gave negative results. The patient weighed 110 pounds, although she should have weighed about 130. Since she had emotional difficulties which required psychotherapy, she was referred for such therapy. Within a few weeks her symptoms, including the cancer phobia, had vanished and she had gained twenty-three pounds. Today she is a healthy, happy person and has avoided useless and traumatizing multiple operations.

Comment.—This patient had emotional and nervous factors whose resolution appeared to be beyond the scope of the surgeon, and she was

therefore referred to a psychiatrist. The clinician and surgeon should remember Hinsie's warning:¹⁵

The aim of psychotherapy from the standpoint of the nonspecialist should be restricted to the treatment of conscious material. Many of the patients whom he sees can be cured by psychotherapy of that part of the mind known as the conscious. The unconscious, that is, the hidden part of the mind, is the province of the specialist, is the province of those who are well familiar with the structure and function of the unconscious.

CASE 4.—H. F. B., a white man aged 52 years, married, a lumber salesman, for the past eight months had had pain in the upper part of the abdomen. Food might aggravate the distress but just as frequently served to allay it. The type of food seemed to have no bearing on the situation. Belching and bloating were frequent. During the previous six months the patient had lost twenty-one pounds. Insomnia occurred repeatedly. Six years before, after a diagnosis of cholelithiasis, chronic cholecystitis, and interval appendicitis had been established, a cholecystectomy and appendectomy were performed.

The patient's father and paternal grandmother had died of gastric carcinoma, and a paternal aunt had died three years after a mastectomy for a malignant tumor. The patient insisted that he, too, must have a cancer because of the abdominal symptoms and loss of weight.

Examination disclosed definite epigastric distress, but no mass was palpable. Roentgenograms of the gastrointestinal tract showed nothing abnormal except a slight deformity of the duodenal bulb, which the roentgenologist interpreted, not as an ulcer, but rather as the result of adhesions to the gall bladder previously removed. An electrocardiogram and basal metabolic studies gave normal results. Routine examination of the blood, stool, and urine showed nothing abnormal.

The patient was informed that no organic cause for his symptoms had been found. He demanded an immediate exploratory laparotomy because he was sure there was a tumor which had not been revealed by the films. Surgical intervention, we assured him, was not indicated.

Detailed inquiry revealed several factors which suggested an emotional rather than a somatic causation of his symptoms. His family's history of malignancy was definitely preying on his mind. The financial depression had all but wiped out his modest fortune, and his business had fallen off. His wife was in the throes of the menopause, with its accompanying depression, flushes, and extreme irritability. His 83-year-old mother lived in his home and needed almost constant attention.

The relation of the patient's numerous anxieties and worries to his abdominal complaints via the autonomic nervous system was explained. His wife was given the necessary estrogen therapy and soon was much improved. The mother was sent to live with a sister. The importance of accepting reality and making the best of it was impressed on the patient during a number of visits to the office. His attention was repeatedly directed to the fact that there was no physical cause to account for his symptoms. The futility of an exploratory operation was re-emphasized.

The abdominal discomfort gradually decreased, with only an occasional flare-up. The twenty-one pounds lost were regained, plus an additional five pounds. The insomnia disappeared after several weeks and has not recurred. When last observed, the patient had been symptom-free for many months. Now and then he would have slight abdominal distress or a brief period of belching, which could invariably be traced to an emotional upset. His wife, now in excellent health herself, recently stated that he was feeling fine and apparently had decided that no malignant growth existed.

Comment.—In this case an exploratory operation might well have resulted in serious emotional trauma. The original symptoms would undoubtedly have persisted, as in Case 3, and might even have been aggravated.

CASE 5.—R. K., a white man aged 34 years, of Irish ancestry, an office administrator, complained of pain after eating, sensitivity in the lower left part of the abdomen, and constipation, all of many years' duration. The distress might disappear from the abdomen, only to recur several hours later, and might even migrate to the chest. Fatigue was always present. The history disclosed that the patient had been nervous for many years. Various physicians had prescribed rest, medication, and vitamins, but these gave little help. Even when the patient was on vacation the symptoms persisted. He was convinced that he had a tumor which could be discovered and removed only by surgical operation. He had been referred to me by a patient who had had a cholecystectomy performed, with an uneventful recovery and convalescence.

Complete physical examination and routine laboratory studies were carried out. In addition, roentgenograms of the gastrointestinal tract and gall bladder, an electrocardiogram, and basal metabolic studies were undertaken. The results were negative.

Merely to inform the patient that his symptoms had no organic cause would have been to leave his symptoms unchanged. It was essential to go a step farther in the investigation. The lead of nervousness recorded in the history was followed, and it was learned that the patient had always been upset emotionally after criticism, chastisement, or ridicule. When he was a boy his father had dominated him and had been critical and unkind. Visits to the home of his parents were still accompanied and followed by abdominal distress. In high school, in college, and at work, censure, reproof, fault finding, and too critical analysis of his accomplishments invariably precipitated abdominal distress or a burning sensation at mealtime.

The patient's intelligence would have been insulted if he had been told that there was nothing wrong, that he should go home and forget his symptoms. The fact that no organic cause could be found to explain the presence of pain did not mean that the pain was not present. Certainly surgical intervention was contraindicated.

On several subsequent visits to the office the patient's attention was directed to the fact that his discomforts appeared to be directly related to emotional reactions of inadequacy. He had been frustrated in his relations with his father, with his teachers, and now with his office associates. Feelings of frustration were present whenever he felt that unnecessary or unjust criticism was being leveled at him. He invariably blossomed under praise. A feeling of inadequacy had been built up as a result of the repeated emotional trauma.

It was explained to the patient how his gastrointestinal tract was involved by the autonomic nervous system in the expression of his emotions. He was guided toward a constructive acceptance of criticism. He was encouraged not to allow criticism to register as an emotional blow, to take it as a passing remark rather than as a personal affront.

CASE 6.—Mrs. C. E. R., a white woman aged 67 years, of Irish ancestry, complained of nausea and of pain in the abdomen shifting from the upper quadrants, especially the left, to the lower quadrants. These symptoms had been present for several years but had been more pronounced the past four or five months. The patient said she frequently felt tense, "as though in a vise."

The patient was well nourished and not acutely ill. Physical examination revealed vague tenderness over the right lower quadrant and a large smooth mass to

the right and independent of, but adherent to, the uterus, probably an ovarian cyst. Complete roentgenologic studies of the gastrointestinal tract and the gall bladder gave negative results, as did all laboratory investigations.

With some hesitation the patient revealed that she had had coitus with her husband several months before, after ten years of abstinence. She felt certain that something had happened in the vagina, a tear or inflammation. Shortly thereafter she consulted a physician, who discovered a mass in the lower part of the abdomen and informed her, in jest but with a straight face, that she must be pregnant. After successive examinations he told her that the mass was growing larger, but he made no further mention of pregnancy.

With trepidation in her voice, the patient said she was sure that she was pregnant, with a freak pregnancy, and that the doctors would not tell her. She recalled reports that children of 5 and 9 years had become pregnant—why not a woman of 67? "And that would be awful, doctor!" She admitted that she had always disliked coitus. Considerable time and patience were taken to explain that no pregnancy or vaginal lesion existed, and during the next several days the patient showed great improvement. There had been no symptoms from the ovarian cyst, and the psychosomatic symptoms disappeared. One week later a periovarian cyst 15 cm. in diameter was removed, and the postoperative course was remarkably free from complications. The patient was discharged thirteen days later, feeling healthier and happier than she had been in years. She has since been seen several times and continues in good emotional and physical health.

CASE 7.—Mrs. E. R., a white woman aged 36 years, an American of Lithuanian ancestry, complained of pain in the right lower quadrant and the lower part of the spine. She believed that this pain was due to an ovarian cancer. Burning pains, like those of rheumatism, occurred in the upper part of the chest, both front and back. There were urinary frequency and diarrhea, and belching occurred after meals. The patient had frequent attacks of cardiac oppression and palpitation, with vertigo. She had a fear of impending disaster, that she might collapse and no one be present to give aid. She stated that she had always been nervous but that during the past two years the symptoms listed had become much more severe.

The history disclosed that two years earlier a sister had died and that, shortly thereafter a second sister had committed suicide. From that time the patient had frequently been troubled with insomnia and with unpleasant dreams of these sisters and of the cemetery where they were buried. Her mother had impressed her with the superstition that dreaming of the dead, especially in the immediate family, meant that another death in the family was sure to occur. The patient was convinced that she would be the next to die, and she had frequent fits of crying and depression.

Complete physical examination revealed no pathologic change except a large cyst of the right ovary. This cyst could not possibly have accounted for the long list of symptoms. Laboratory examinations revealed nothing significant. Complete roentgenologic studies of the gall bladder and gastrointestinal tract gave negative results except to show moderate spasticity in the descending portion of the colon.

The lack of physical findings except for the ovarian cyst was explained to the patient, as was the impossibility that her many symptoms could be related to the cyst. The fact that her disability was out of proportion to the disease present was emphasized. A number of consultations were needed to convince her that her symptoms had no somatic foundation but originated in her basic fears, conflicts, and apprehensions. Time and patience were taken to explain that the autonomic nervous system influences the heart, stomach, colon, bladder, and other pelvic organs, and that anxiety and worry had resulted in certain reactions in these organs,

producing the symptoms of which she had complained. Gradually, after reassurance and repetitive discussion of her emotional fears, her various complaints disappeared.

The ovarian cyst, which proved to be 13 cm. in diameter, was then removed, and the patient made an uneventful recovery. The only symptom which remained was occasional pressure and pain in the right lower quadrant. Both the patient and her husband state that they cannot recall when she has been as healthy, happy, and cheerful.

Comment.—Obviously the bizarre symptoms could not have been caused by a simple ovarian cyst, the only lesion present. To have operated before eliminating the psychosomatic symptoms would have been to risk continuation of these symptoms and possibly another operation because of the cancer phobia. The patient's new understanding of the psychodynamic implications served to clarify the basis of her fears and thus to eliminate them.

SUMMARY AND CONCLUSIONS

Psychosomatic symptoms in patients who consult the surgeon must not be overlooked or ignored. They are as real and as significant as are the symptoms which are organic in nature. They are the expression of emotional disturbances, manifested via the autonomic nervous system as organic complaints. To tell the patient to forget them, and to do nothing to relieve them, is to neglect a vital phase of the art of healing.

Psychogenic symptoms frequently simulate the effects of organic, operable lesions. The surgeon, therefore, sees many patients who present them. By recognizing them for what they are—neither evidence of a somatic disease process unverified despite physical and laboratory investigations, nor evidence of a true neurosis—he will avoid needless surgical procedures and save his patient much mental and physical sufferings.

When a patient is found to have an operable lesion, but one which could not possibly be the cause of all his many complaints, it is extremely important to clarify the unrelated symptoms before the necessary surgical procedure is undertaken. Otherwise these may well persist after operation, and it will be a difficult task indeed to convince him that he does not have a lesion which was overlooked at operation.

Cases cited from a surgical practice illustrate some types of psychosomatic symptoms which a surgeon is apt to encounter, and detail a variety of causative factors and methods of dealing with them in order to secure for the patient improved mental and physical health.

REFERENCES

1. Grinker, R. R: There Is Nothing Physically the Matter, J. A. M. A. 117: 1377, 1941.
2. Weiss, Edward, and English, O. S.: Psychosomatic Medicine, Philadelphia, 1943, W. B. Saunders Company.

3. Dunbar, Helen Flanders: Psychosomatic Diagnosis, New York, 1943, Paul B. Hoeber, Inc.
4. Christian, H. A.: Osler's Principles and Practice of Medicine, ed. 14, New York, 1942, D. Appleton-Century Co., Inc.
5. Alvarez, W. C.: Indigestion and Pain, New York, 1943, Paul B. Hoeber, Inc.
6. Book review, J. A. M. A. 124: 470, 1944.
7. Smith, L. A., and Rivers, A. B.: The Treatment of Uncomplicated Duodenal Ulcer, J. A. M. A. 122: 209, 1943.
8. Wakefield, E. G., and Mayo, C. W.: Functional and Sociologic Disorders of the Colon, J. A. M. A. 111: 1627, 1938.
9. Brooks, Barney: Psychosomatic Surgery, Ann. Surg. 119: 289, 1944.
10. Editorial: Psychotherapy in Gynecology and Obstetrics, J. A. M. A. 109: 1366, 1937.
11. Whiteacre, F. E., and Barrera, Benjamin: War Amenorrhea, J. A. M. A. 124: 399, 1944.
12. Douglas-Wilson, Ian: Somatic Manifestations of Psychoneurosis, Brit. M. J. 1: 413, 1944; cited, editorial, J. A. M. A. 125: 279, 1944.
13. Rowntree, L. G.: National Program for Physical Fitness, J. A. M. A. 125: 821, 1944.
14. Menninger, W. C.: Neuropsychiatry, J. A. M. A. 125: 1103, 1944.
15. Hinsie, L. E.: A Clinical Description of Psychosomatic Medicine, M. Clin. North America 28: 525, 1944.

IODINE AND THYROIDISM

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HISTORICAL

BERNARD CURTOIS while experimenting in the extraction of alkali from seaweed, discovered iodine (1811).

After Fyfe had isolated iodine from sponges, Jean Francois Coindet (1820), of Geneva, maintained that the element is the active constituent of burnt sponge and is effective as a remedy for diseases of the thyroid.

Trousseau (1868) experimented with the use of tincture of digitalis instead of iodine, in the treatment of goiter.

Plummer (U.S.A.) was the first to popularize the use of iodine in exophthalmic goiter.

Charles Edouard Brown-Séquard, in 1889 (antedated by Ruysch, Johannes Müller, and others), made an epochal report to the Biological Society of Paris. His experiments indicated that the ductless glands furnished substances to the blood which influenced the organs of the body to a pronounced degree.

In 1895, Magnus-Levy fed dried animal thyroids to normal men and made the original observation that their metabolic rate was considerably increased.

From about 1893 onward, he used the Zuntz-Geppert technique in his estimation of the metabolic rate, with the realization that the effect of disease on metabolism could not be appraised without the study of normal controls.

It thus became evident that the gland must contain a potent chemical substance able to influence many other organs. Kocher prophetically suggested that this substance might contain iodine, which was known to have beneficial effects when given to cretins. Somewhat later (1896) Baumann discovered that the thyroid contained large amounts of iodine in combination with organic substances, chiefly globulin. This he denominated iodothyron (later thyroiodine) and showed that from the purest thyroiodine 9.3 per cent of iodine could be obtained in crystalline form.

As a result of the work of Kendall (1913-1919) and Harington (1926-1930), a pure chemical substance was finally isolated from the thyroid gland. Kendall named it "thyroxine." When this substance was injected into men (or beasts) the symptoms of hyperthyroidism were produced.†

Received for publication, Nov. 2, 1944.

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†Journal of Experimental Medicine, 1915.

HISTOLOGY AND PHYSIOLOGY

It must be recalled that the units of thyroid tissue are glandular vesicles or acini which are lined by a layer of epithelial cells. They remove iodine from the blood and convert it into an active hormone. A constituent of this hormone, thyroxine, was identified and later synthesized.

Among the factors which influence the functional activity of the thyroid are the amount of available iodine for synthesis and the pituitary thyrotropic hormone. The substance formed by the thyroid cells passes into the lumen of the vesicle where it is stored as a colloid. This is resorbed through the thyroid cells and sent into the blood stream.

The histologic structure of the gland is a gauge of its functional activity. Inadequate activity, or overactivity, may consequently be evidenced by histologic examination. Not only is the activity of the normal thyroid tissue cyclic, but in diseased thyroids different parts of the gland may show different degrees of function or actual dysfunction.

Dr. Joseph G. Hamilton, Dr. Mayo H. Soley, and Dr. Carl B. Eichorn, of California University, described a method by which it is possible to correlate the deposition of administered iodine in the thyroid with the histologic structure of the gland. They wrote as follows:

Two days after the administration of a radioactive isotope of iodine the thyroids were extirpated and sections were prepared from the glands. The sections were placed against photographic plates on which the beta radiation from the accumulated radio iodine produced areas of darkening. These images made a pattern of the distribution of the stored radio iodine in the sections of thyroid tissue. Each exposed film was compared with its corresponding section under a microscope. This technique was employed to compare the deposition of the administered radio iodine with the histologic structure of the thyroid tissue obtained from five patients with nontoxic goiters, two patients with carcinoma of the thyroid, and two patients with hyperthyroidism. In all the varieties of thyroid tissue examined the areas of hyperplasia were found to have the greatest ability to concentrate the administered radio iodine. This phenomenon was most clearly shown in the glands of patients with nontoxic goiters. . . The selective accumulation of radio iodine by hyperplastic thyroid tissue indicates that this radio-active element may be of therapeutic value in hyperthyroidism.*

It has been shown time and again that the follicular cell is the unit of thyroid function and may undergo, like all large and minute tissue entities, hypertrophy and hyperplasia with increased activity. This unit appears to be the prime factor in thyroidal physiology and pathology. Under normal conditions the cell is cuboidal, with clear cytoplasm and a nucleus situated near its base. This appearance is subject to slight variations largely dependent on the degree of glandular activity. At rest the cell is readily stimulated (particularly by iodine)

*Publication in Pharmacology, University of California.



Fig. 1.—A 27-year-old white man with a basal metabolic rate of plus 49 after iodine therapy. Pathology: There is marked hyperplasia of the cells lining the follicles, and many papillary infoldings extend into the lumen. There is diminution of colloid, and the margins along the cell border are irregular. (U. S. Army Medical Museum Negative No. 75852, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)

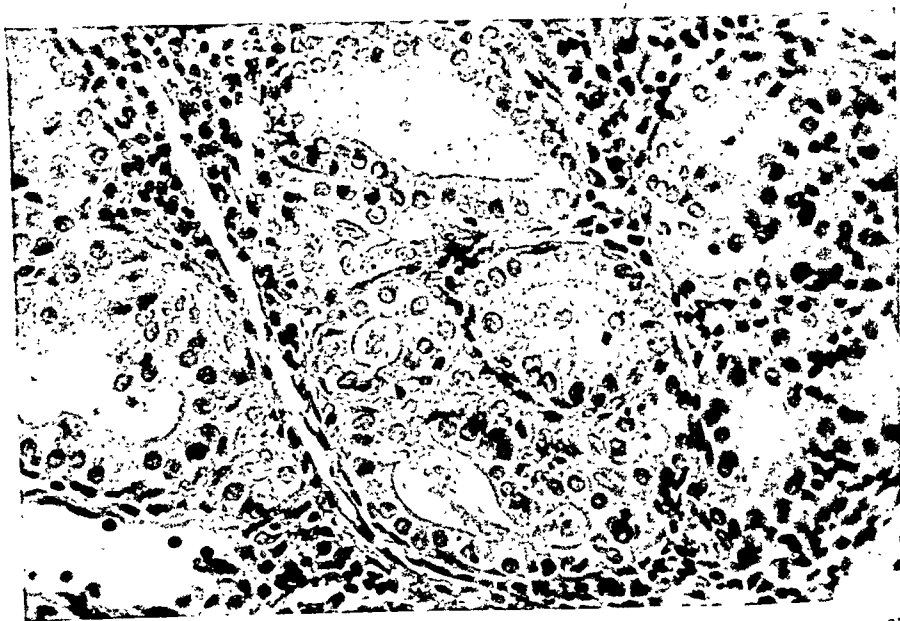


Fig. 2.—A 22-year-old white man who had a basal metabolic rate of plus 65, which fell to plus 31 after iodine therapy. Pathology: In most of the follicles the colloid is diminished or absent. The follicular epithelial cells are enlarged and tall. Most of the follicles are evenly rounded, and little papillary projection is seen. In a few areas the epithelium is flattened and no colloid is present in the follicles. There is a lymphocytic infiltration throughout. (U. S. Army Medical Museum Negative No. 75851, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)

and in consequence becomes columnar, with its cytoplasm granular and its nucleus elevated. This mutation likewise occurs through glandular activity which obtains at puberty, menstruation, and pregnancy. A decreased intake of iodine results in an increased colloid storage. The cell then loses its cuboidal form, becoming flat. The cytoplasm is almost indistinguishable and the nucleus, magnified, appears to occupy the cell in its entirety. This has been denominated the "inactive or resting stage." In an advanced phase the nucleus is faintly visible, the cytoplasm poorly stained, and the cell properly flattened.



Fig. 3.—A man 31 years old, with a plus 70 basal metabolic rate, received iodine for seventeen days prior to surgery. Pathology: This section shows alternating areas of hyperplasia and involution. Compare the height of the flattened epithelium of the involution follicles with that of the tall hyperplastic cells. (U. S. Army Medical Museum Negative No. 75854, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)

The variety of epithelium lining the follicles is the most important index of thyroid activity. It is clearly axiomatic that: (1) Tall columnar epithelium resorbs hormone from the follicular lumen and discharges it into the blood stream; (2) high cuboidal epithelium actively produces colloid; (3) low cuboidal epithelium produces colloid slowly; (4) low, flat epithelium is inactive. (See Figs. 1 to 5.)

The height of acinar epithelium, therefore, acts as a measure of functional activity and in all probability also as a functional measure of the thyrotropic hormone of the pituitary. Marine and Lenhart, writ-

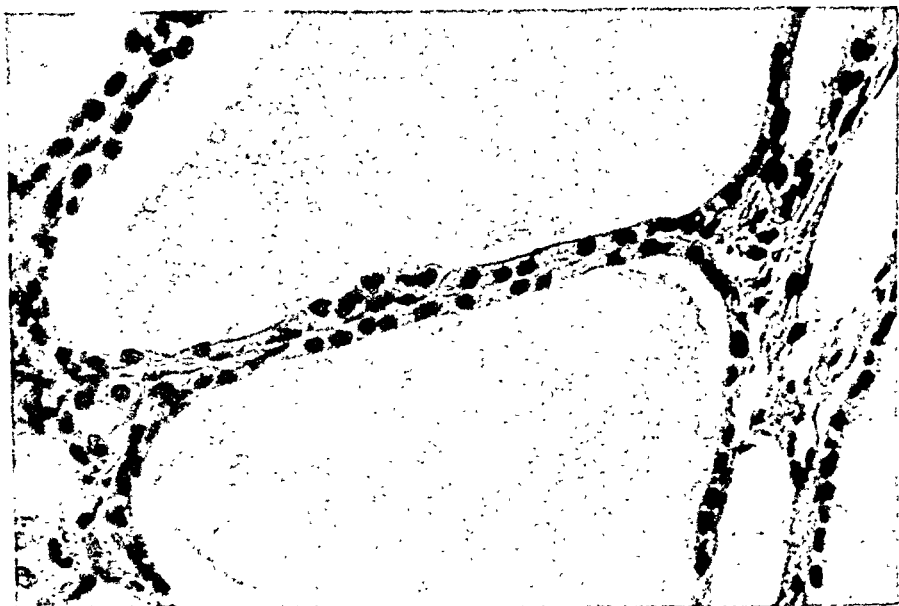


Fig. 4.—Flattened epithelium of involuted follicles seen in Fig. 3 (U. S. Army Medical Museum Negative No. 75825, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)



Fig. 5.—A 39-year-old white man. Basal metabolic rate was plus 45. Pathology: The follicles and their epithelium show all stages of transition from the hyperplastic to the normal. The unusually large follicles distended with colloid are hyperinvoluted. In some areas the epithelium is abnormal and resembles the types seen in some adenomas. (U. S. Army Medical Museum Negative No. 77415, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)

ing of the thyroid-pituitary relationship, concluded that the thyroid secretion affects the pituitary to the same degree as the thyrotropic principle of the pituitary affects the thyroid* Herring found that the neural posterior lobe of the pituitary is also involved in hyperthyroidism.†

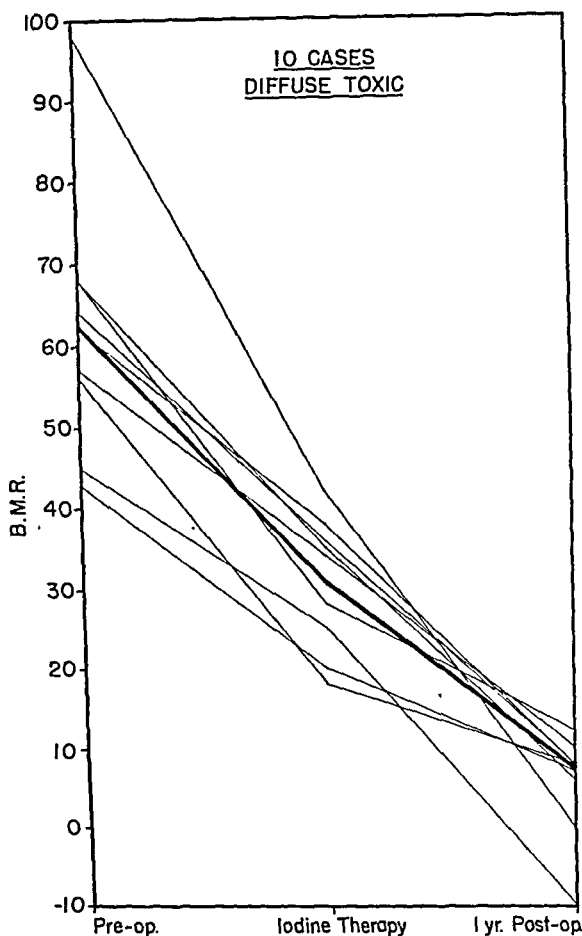


Fig. 6.—Graph of ten typical cases of diffuse toxic goiter (hyperplasia) illustrating the effect of iodine therapy and surgery on the basal metabolic rate.

It is obvious that the iodine content of the gland is the determinant factor in its activity; if the total is adequate there is no dysfunction but if it drops below a specific level, accelerated activity and hyperplasia are exigent for physiologic requirements.

It is of interest to note that the thyroid glands of fetuses and of newborn infants are iodine-free. The gland in herbivora has a high iodine content, while that of carnivora has the lowest iodine content (Baumann, Ross, and Oswald).

*Archives of Internal Medicine, 1911.

†Proceedings of Royal Society of Medicine, 1921.

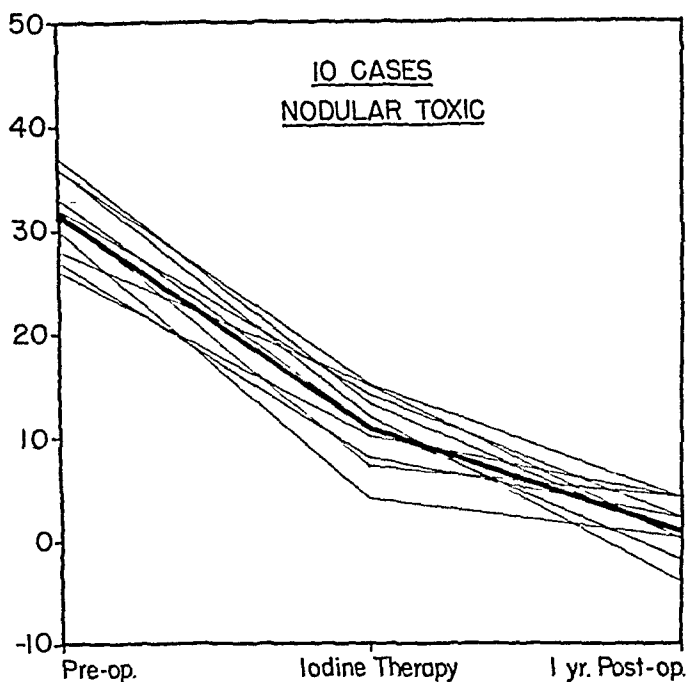


Fig. 7.—Ten cases of nodular toxic goiter (adenomatous) illustrating the results obtained in reduction of basal metabolic rate after preoperative iodine administration followed by surgery.

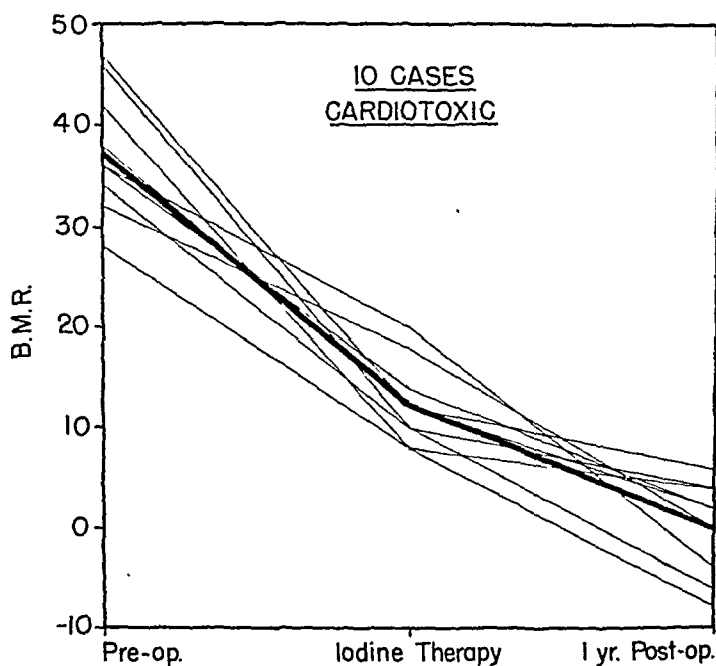


Fig. 8.—Reduction of basal metabolic rate in ten cases of cardiotoxic goiter (Hertzler) after iodine therapy and surgery.

The basic function of the thyroid is the production of thyroxine to maintain the metabolic rate higher than it would be otherwise and through variation in activity to alter the metabolic rate in accordance with physiologic needs. Recent investigations have shown, however, that the symptoms of increased thyroid activity caused by hyperplasia of the gland are not invariably accompanied by a raised basal metabolic rate. (See Figs. 6 to 9.)

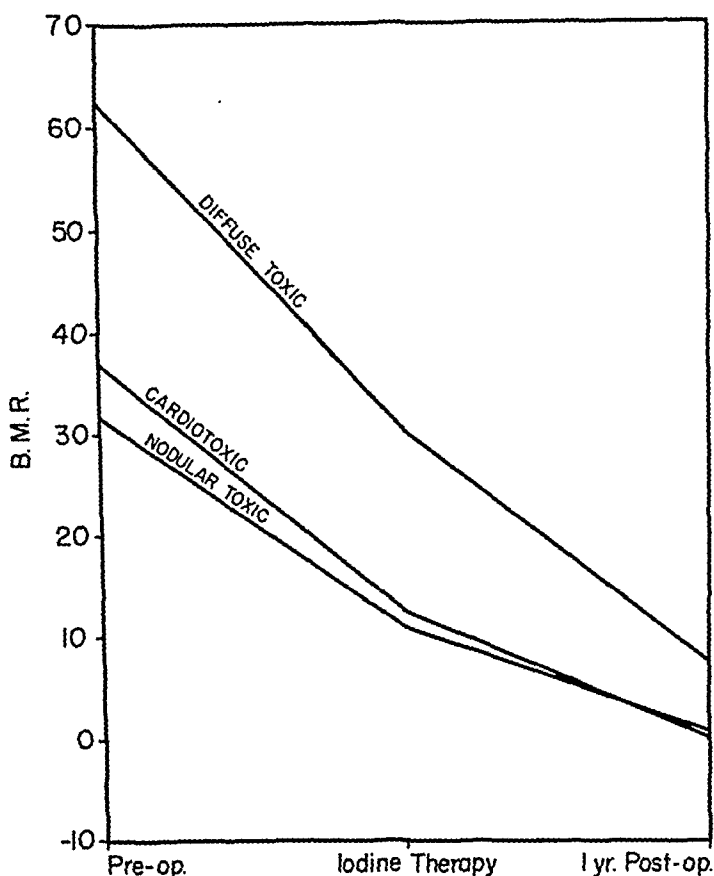


Fig. 9.—Composite graph of Figs. 6, 7, and 8.

With a total cessation of thyroid function the oxygen consumption or basal metabolic rate falls to 40 per cent. Incidentally, 1 mg. of thyroxine causes an increase in metabolism of about 1,000 calories in a normal person.

The thyroid hormone is present in its highest concentration in the thyroid gland but has been found in nearly all body tissues, including the skin, and in the body fluids. In the blood 60 per cent of iodine is alcohol-insoluble (thyroxine) and 40 per cent alcohol-soluble. This balance, however, is disturbed in thyroid disease; in hyperthyroidism, for example, there is a relative increase in the alcohol-insoluble fraction.

The normal thyroid contains 10 mg. of iodine at a concentration of 40 mg. per cent by weight. This is largely present in the colloid. The normal iodine content of the blood is 12 micrograms per cent. This indicates that the normal blood contains 120 parts of iodine per billion. The blood iodine is increased in patients with hyperthyroidism and is less in normal persons. (The normal daily iodine requirement is about 0.2 mg. per day; the average amount actually taken on ordinary diets is about 1.0 mg. per day.) After administration of iodine there is an increase in the iodine content of the thyroid. Administered iodine becomes stored and firmly bound within the thyroid almost instantaneously, but in some obscure form, not as thyroxine, for synthesis of the latter requires a number of hours (Fig. 10).

It is known that iodine and thyroid function are interdependent because the gland is the principal storehouse of the element. So far as is known it is the only organ capable of elaborating an iodine-containing substance.

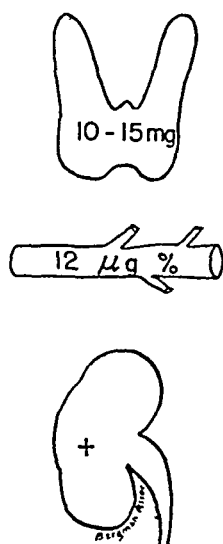


Fig. 10.—Iodine content of thyroid, blood, and urine in a normal individual.

The fundamental features of iodine metabolism in exophthalmic goiter are the following: (1) In untreated patients the thyroid gland iodine is lessened; (2) the blood iodine is usually increased in untreated persons; (3) the urinary excretion of iodine is ordinarily increased; (4) exophthalmic goiter reveals a progressively decreasing iodine balance. However, patients with toxic nodular goiter present an even greater negative iodine balance due to a greater urinary excretion, and immediately following thyroidectomy a rise occurs in the blood iodine of noniodinized patients, whereas there is a decrease in those treated with iodine (Figs. 11 and 12).

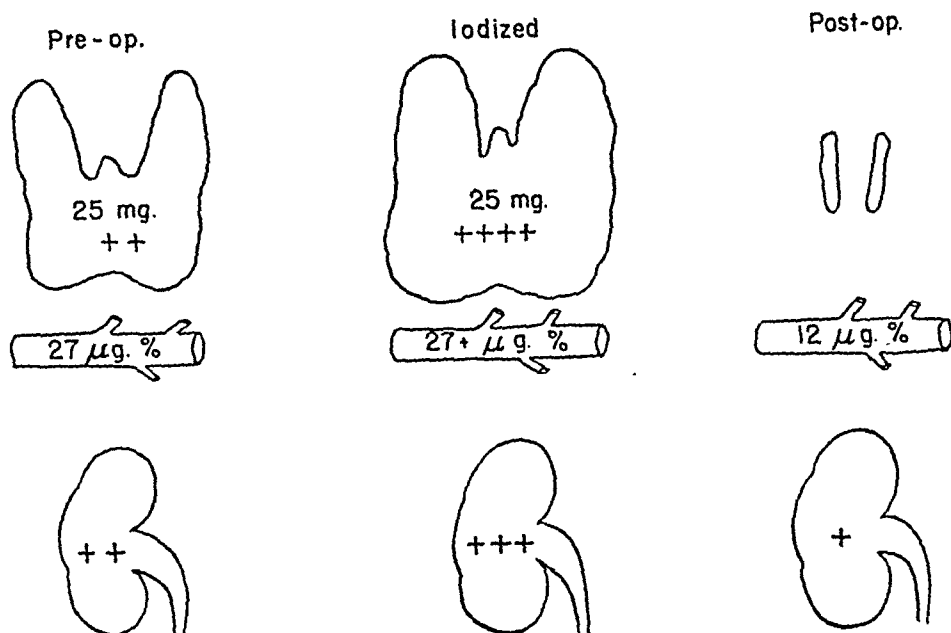


Fig. 11.—Iodine metabolism in individuals with diffuse toxic goiter (hyperplasia).

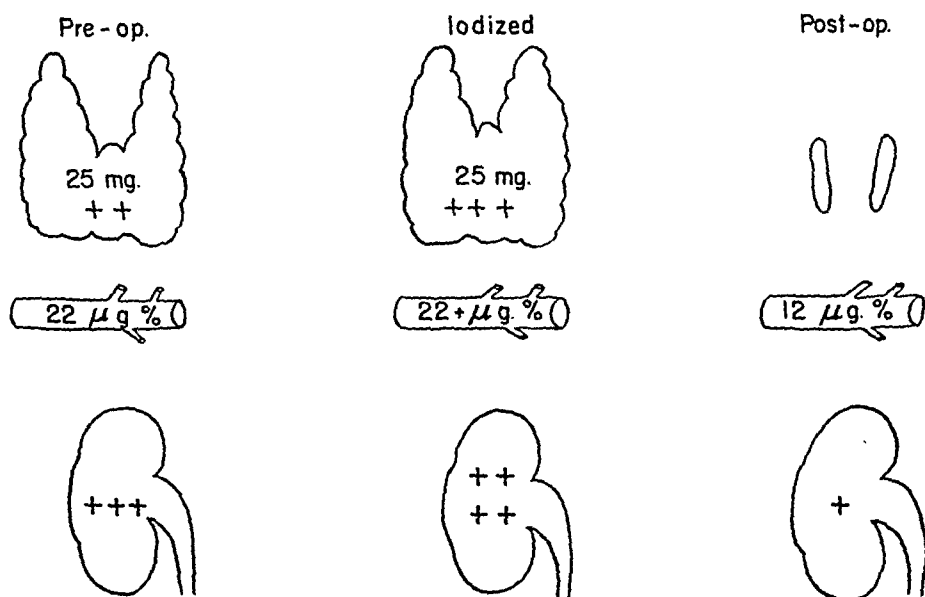


Fig. 12.—The iodine content that prevails in a nodular toxic goiter (adenomatous), preoperatively, before and after iodization, and postsurgically.

PATHOLOGIC PHYSIOLOGY

A dissident view concerning the cause of hyperthyroidism is that it is not always due to an accumulation of iodine. The thyroid gland, it is argued, normally contains a certain amount of iodine stored as an inert compound. A gradual disintegration takes place, according to the requirements of the animal economy. This assumption has many physiologic parallels in fibrinogen, mucinogen, glycogen, and all other substances by which a material is stored inert until required. It is common knowledge among physicians that the amount actually present, though not great, is fairly constant in health; that the intake is necessarily variable and precarious; and the normal excretion so small that, in our day, the matter remains purely conjectural. It is obvious, then, that some physiologic provision should be made for the preservation and retention in the body of such an essential element, the supply of which is so precarious. Succinctly stated, the same iodine is used repeatedly, being freed from the thyroid storehouse to perform its functions, one of which is that of acting as a lime carrier, and returning empty to the thyroid where it again enters into suitable combination and is again stored until required. Under these conditions, to pursue this theory further, it seems probable that hyperthyroidism is the result of an excessive discharge of the reserve iodine into the system by the chemical disorganization of the substance which normally holds it in storage. The iodine thus cast into the system produces hyperthyroidism. Thus, a sudden explosion in the iodine stores of the thyroid gland is all that is needed to flood the system with iodine and start the afore-mentioned disease. This is probably what occurs when the disease is started by fright or sudden shock. Psychic trauma and emotional upsets often start symptoms of toxicosis doubtless owing to the interdependence of the diencephalon and the pituitary. Nevertheless, it is known that hyperthyroidism is responsible for the stimulation of psychic emotions.

It is obscure by what means iodine is normally set free from the thyroid gland, though it is assumed that it is governed by laws of chemistry which are under the control of nervous impulses.

THERAPY

Therapeutic effects of iodine are extremely variable. There is an optimum amount suitable for different patients.

Iodine administration brings about a striking amelioration of the condition but the improvement disappears when the iodine is withheld. If iodine is continued indefinitely the disease is milder than otherwise, but it is not of shorter duration.

Some thyrotoxic patients grow progressively worse under iodine medication because the amount of iodine administered is actually inadequate. As soon as the optimum increase of iodine is found, the syndrome, with

the associated disturbed metabolism, is checked and regresses. This does not carry the implication that it is best to begin treatment with large doses of iodine. It is advantageous to start with a small dose, 10 mg. of Lugol's solution, for example, and then to observe the reaction. If this proves ineffectual the dose should be rapidly increased until the optimum amount is found for the specific patient. It is well to bear in mind, incidentally, that on rare occasions an apparently inadequate dosage may induce a refractory phase in the therapeutic regimen.

There is still a sharp difference of opinion among clinicians as to what constitutes a small dose of iodine. It is estimated that 6 mg. daily is a needful amount of iodine to induce maximum colloid accumulation in the normal thyroid gland. Smaller doses, it has been shown, appear to be insufficient to induce a maximum storage. It is clear, therefore, that 6 mg. daily is a sufficient dosage in the treatment of thyrotoxic goiter. Many investigators, however, have found that this physiologic dosage frequently proves ineffective.

Admittedly, a certain number of thyrotoxic patients, for occult reasons, appear to be iodine resistant. The resistance is not solely against iodine. It is also true of the prolonged use of various glands of internal secretion.

It has been maintained that the refractory influences are induced either by the formation of substances which neutralize the utilized iodine, or by antihormones, if endocrine substances have been given. This is brought about by a self-regulatory mechanism which counteracts the effects of the substance used therapeutically.

It is conceivable that some patients who are "lugolized" for a time become intractable to iodine. There are those, too, who are iodine resistant under all circumstances.

It has been maintained that the intractability in question, which occurs after prolonged use of iodine, is due to prolonged medication, with a consequent exhaustion of the thyroid, evidenced by the total disorganization of the parenchyma of the gland noted macroscopically and microscopically. The gland is consequently unable to assimilate iodine and thus there is a failure of therapeutic effect.

Means wrote that there is no true refractoriness to iodine and that the only patients who really do not respond are those who are not thyrotoxic, or if so, are already iodinated. Of all patients in his series, only 3 per cent apparently failed to respond; this small group was explained by a rapid increase in severity of the disease occurring at the time the iodine was given. A poor response to iodine, he holds, is indicative of a poor surgical result. In ward cases of the Massachusetts General Hospital, over a ten-year period, reported by Means, the mortality of patients who responded well to iodine (97 per cent of all cases) was 1.1 per cent; in those who did not respond well (3 per cent of all cases) the mortality was 27.3 per cent.

The physiologic and chemical role of iodine in thyrotoxicosis is still shrouded in a veritable theoretic fog. This is also true of the frequent return of the syndrome to its previous or more advanced stage after a few weeks of iodine medication. And still seeking a scientific explanation is the answer to the question: "Why does iodine induce a specific response in thyrotoxicosis—a response which is absent when iodine is administered to normal persons?" This response in thyrotoxicosis makes confusion more confounded in that it is absent in experimental hyperthyroidism when thyroid extract is used in men and beasts, as was shown by Carson, in 1928.

The following factors must be considered in an attempt to elucidate the multifarious effects of iodine administration in thyrotoxicosis:

1. De Ligneris, Marine, and many other investigators, have given this aspect of the quest profound study. It is now widely accepted, in fact, axiomatic, that iodine increases the alveolar colloid content. This substance apparently thickens, and thereby distends the walls of the repository, of which the cells and their nuclei flatten and elongate in the process. The interstitial cells are strikingly diminished in size and number.

2. In the diffuse thyrotoxic parenchymatous goiter the colloidal iodine is quantitatively inadequate and excreted into the blood, and ultimately, into the lymph stream. The iodine reserve of the thyrotoxic gland is consequently lessened and obviously the blood iodine is relatively increased. However, the glandular iodine is largely ionized and inorganic, while the organic fraction in the blood is increased. It is the ionized inorganic iodine which is thyrostimulant, as shown by Saegesser, in 1932. It may be argued that under favorable, or unfavorable, regional and physiologic influences the stimulation may, in a manner of speaking, cause the gland to run amuck.

3. Iodine when supplied to a thyrotoxic gland is adequately stored and utilized to a degree where physiologic needs are satisfied. The relation of the various fractions of thyroid return to normal, the colloid is again in reserve, and there is stabilization of thyroidal function. This is largely proved by the clinical behavior of the patient and specifically by the absence of thyroidal manifestations. The soft, elastic consistency of the gland is changed to a distinctive firmness consequent upon the alveolar storage of colloid. These units, as previously stated, become distended to capacity. This is what is known as the "thyroid response" to the ingestion of iodine. *It is a physiologic phase.*

4. Another well-nigh paradoxical effect frequently noted is not only the recrudescence, but the augmentation, of thyroidal symptoms despite the continued use of iodine. An apparently valid explanation is that the element, having accomplished its physiologic purpose, is no longer required, except in the mere maintenance of physiologic function.

When the increased iodine supply is kept up the effect goes into reverse, becomes pathologic, with a train of toxic symptoms.

5. Iodine therapy is less effective in thyrotoxic nodular goiter than in the diffuse parenchymatous variety. This is because the degree of cellular hyperplasia is greatly reduced in the latter condition. The large colloid nodules present are only moderately influenced by iodine administration. They do not readily yield their large thick colloid reserve as in the easy manner of the alveoli in the diffuse parenchymatous form of goiter. It is thus clear why thyrotoxic nodular goiter responds to a less degree to iodine than the diffuse parenchymatous forms, in which the cellular elements are hyperplastic and overactivated.

6. Iodine is not a cure for thyrotoxic goiter, but in most instances induces a resting phase so that the patient is "safe for surgery."

7. Prolonged iodine medication, especially with high dosage, frequently results in thyrotoxicosis.

8. Again, this may induce a refractory state.

9. Nevertheless, iodine medication is indicated in all varieties of thyrotoxicosis.

10. The ideal medicament for thyrotoxic patients with cardiac manifestations is iodine. Thiouracil,* recently discovered, may have some value as a depressant of thyroid function. "The daily administration of 1 to 2 Gm. of thiourea or of 0.2 to 1 Gm. of thiouracil to hyperthyroid persons," wrote Astwood, "resulted in the relief of symptoms and the return to normal of the serum cholesterol and the basal metabolic rate." This medicament must for the present be used with caution.

11. The success of iodine treatment depends upon the rapidity with which an adequate dosage can reduce the enhanced oxidative processes in thyrotoxicosis.

12. Iodine is not only useful as a temporary medication in thyrotoxicosis, but is also a valuable diagnostic means. In doubtful cases it may be employed as a therapeutic test to determine the presence of thyrotoxicosis.

*Astwood, E. B.: Journal of the American Medical Association, 122, 1943.

SUCCESSFUL REMOVAL OF FOREIGN BODY WITHIN THE PERICARDIUM

CASE REPORT

MAJOR THOMAS DUVAL WATTS,* AND MAJOR ELAM C. TOONE,†
MEDICAL CORPS, U. S. ARMY

A SOLDIER was admitted to a General Hospital Sept. 15, 1943, because of recurrent attacks of left shoulder and precordial pain of sufficient severity to prevent him from keeping up with his organization.

In March, 1943, he had been wounded during the battle of Fondouk Pass when a shell fragment entered the left anterior chest at the level of the third intercostal space, just lateral to the sternal border. His next recollection was twenty-four hours later when he regained consciousness in a hospital where he was told that he had been in a shocked and dazed condition. For the next few days he was troubled by a dull aching substernal pain which became sharp and quite severe with deep breathing or coughing. This complaint disappeared spontaneously. On the tenth day after hospitalization he was able to be up and about the ward and remained symptom-free until discharged to full duty with his outfit twenty-six days later. Sixteen days after leaving the hospital, while doing guard duty, he first noted a sharp pain originating in the supraclavicular region of the left shoulder and radiating down over the left chest to the region of the nipple. This pain lasted for a period of twenty-four hours and was comparable to the discomfort experienced in spraining a finger. Associated with this was a dull aching pain originating under the lower portion of the sternum and radiating out to the apex of the heart, lasting about forty-eight hours. Both pains disappeared spontaneously and no medical attention was sought. During the next two months the soldier had three recurrences of shoulder and precordial pain similar in nature and duration to the original episode and occurring during periods of rest or mild activity. Following the last attack, July 4, 1943, he was examined by a medical officer and placed on light duty. He remained in this capacity until Aug. 30, 1943, when he was referred to a General Hospital for further study and disposition because in the opinion of his medical officer he was not able to fulfill the duty requirements of a combat soldier. At that hospital he was observed during two paroxysms of chest and shoulder pain while confined to bed, and in addition it was noted that at times he had short periods of arrhythmia apparently due to runs of extrasystoles usually brought on by change of position. X-ray studies revealed a small metallic foreign body lying adjacent to the base of

Received for publication, July 21, 1944.

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the heart in the region of the right auricle and an electrocardiogram done Sept. 2, 1943, showed a low T wave in Lead 1 with normal findings in Leads 2, 3, and 4 (Fig.1). There was no complaint of dyspnea, ankle edema, or palpitation at any period. Following these examinations, the opinion was expressed that the foreign body should be removed but in another Theatre.

Physical Examination.—Examined at a General Hospital, Sept. 15, 1943, the patient was found to be a well-developed, well-nourished white man lying quietly, flat in bed, comfortable and relaxed.

Head and neck.—Head and neck were found to be normal.

Chest and lungs.—There was a small healed scar 1 by 1 cm. in diameter in the third left intercostal space adjacent to the left sternal border. The lungs were normal to percussion, palpation, and auscultation and the excursion of the thoracic cage was free and equal.

Cardiovascular.—Pulse was 84, rhythm regular, and blood pressure 108/64. Point of maximal impulse was in the fifth left intercostal space 8 cm. from the midsternal line. A grade 1 systolic murmur was heard localized over the pulmonic area and P₂ was accentuated. When the patient was made to roll to one side or sit up quickly, brief runs of extrasystoles were noted which disappeared promptly. There was no distention of the neck veins, no râles at the lung bases, no ankle edema, and the liver was not palpated.

Examination of the abdomen, genitals, extremities, and nervous system was negative.

Laboratory.—Blood count showed red blood cells, 4,600,000; hemoglobin, 14.5 Gm.; white blood cells, 6,800; polymorphonuclears 82 per cent; and lymphocytes, 18 per cent.

Urine, specific gravity was 1.020 and it was negative for presence of albumin, sugar, or significant sediment.

The sedimentation rate was 2.5 millimeters per hour (Wintrobe).

X-ray and fluoroscopic examinations, Sept. 16, 1943,* showed a metallic foreign body 8 by 6 mm. lying 8 cm. beneath the anterior skin, as marked at the time of fluoroscopy, and about 1 cm. to the right of the midline at the level of the lower border of the sixth dorsal vertebra, apparently lying close to or within the pericardial sac near the junction of the superior vena cava and the right auricle. The foreign body moved synchronously with the cardiac contraction and was not influenced by respiration. The lung fields were clear.

An electrocardiogram was made Sept. 20, 1943 (Fig. 2). T waves were inverted in Leads 1 and 4 and occasional ventricular extrasystoles were present in Lead 2. The tracing was otherwise normal. These T-wave changes as compared with the tracing made Sept. 2, 1943 (Fig. 1) at a General Hospital were interpreted as indicating myocardial damage of a progressive nature.

*Fluoroscopic and x-ray examinations done by Lieutenant Colonel C. D. Smith and Captain D. A. Russell.

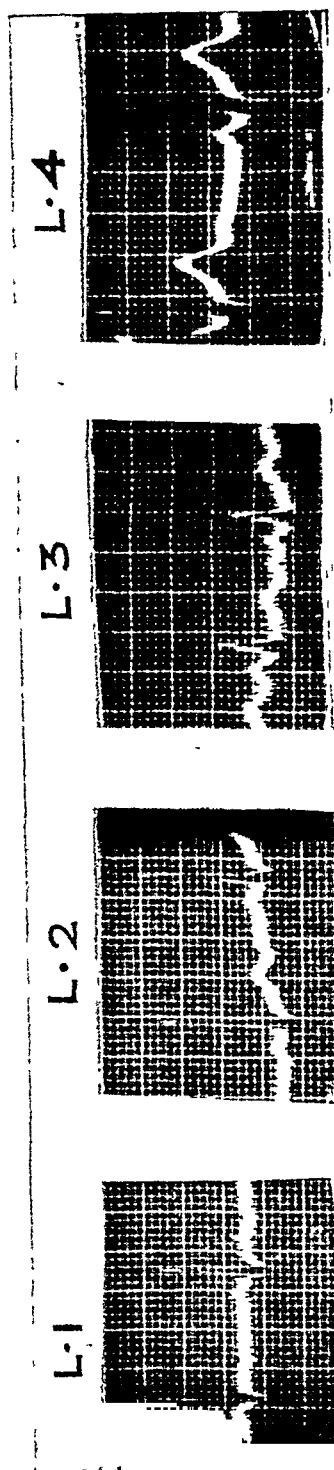


Fig. 1.—Sept. 2, 1943. Normal sinus rhythm. P-R interval 14 seconds; T₁ inverted, T₄ upright.

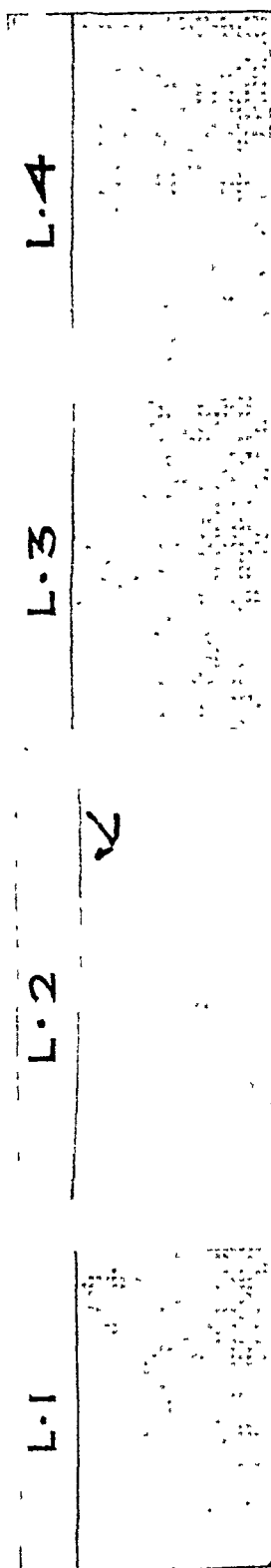


Fig. 2.—Sept. 20, 1943. Rate 70 per minute. Normal sinus rhythm. P-R interval 11 seconds; one ventricular extrasystole present in L₃. T₁ and T₄ inverted.

In light of the evidence presented by these studies we concurred in the opinion that the foreign body should be removed. This decision was reached because there were recurrent episodes of anginal pain which were thought to arise from either the myocardium or pericardium or both, because there were extrasystoles which recurred after exercise or when changing position, because the foreign body was located in the region of the sinoauricular node where minor histologic damage might produce major physiologic dysfunction, and because electrocardiography revealed evidence of progressive myocardial damage over a relatively short period of time. Furthermore, it was necessary to give full consideration to the possibility that the foreign body might erode into the auricle or superior vena cava. Likewise, the danger of secondary infection and extensive adhesion formation at a future date confronted us.

Sept. 26, 1943, while the patient was under observation and confined strictly to bed, he developed the pain in the left shoulder and under the sternum previously described. Associated with this was a temperature elevation to 100° F., a white blood cell increase from 6,800 to 9,600 and a fall in the sedimentation rate from 2.5 to 18 mm. per hour. The electrocardiogram remained unchanged (Fig. 3) and twenty-four hours after the onset of the pain the patient felt perfectly well. The temperature returned to a normal level.

The occurrence of this episode coupled with his previous clinical course made us feel that it would be unwise to delay operation further and preparations were made to remove the foreign body at once.

The operation was performed Sept. 29, 1943, under endotracheal ether and oxygen and one-half of 1 per cent procaine solution locally infiltrated. A right parasternal incision for an extrapleural approach was made extending from the lower border of the second rib along the sternal margin to the fifth rib and the lower border of the fifth rib to the nipple line. The skin-fascia muscle flap was turned up to expose the third and fourth costal cartilages and the anterior ends of the corresponding ribs. The third and fourth costal cartilages and anterior one inch of corresponding ribs were resected subperiosteally. The posterior perichondrium and intercostal bundles were divided near the sternum and retracted to expose the internal mammary vessels which were doubly ligated proximally and distally with No. 1 chromic catgut and resected between the ligatures. The communicating intercostals were also ligated. The pleura was gently separated from intercostal bundles and posterior perichondrium and laterally from sternal border and pericardium. It was necessary to resect a portion of the sternum. The periosteum was separated anteriorly and posteriorly from the area and the bone was then removed with rongeur forceps. The pericardium was incised and the incision extended exposing the right ventricle, right auricle, and superior vena cava. There were soft adhesions between the right auricle and pericardium, right auricle and superior vena cava, and

the upper anterior portion of the right ventricle. These adhesions were separated and a foreign body approximately 1 cm. in length was found encapsulated on the anterior aspect of the right auricle in close proximity to the superior vena cava. The fragment was very gently freed and removed. The pericardium was loosely approximated with interrupted sutures of No. 1 catgut. The incision in the thoracic wall was closed approximating the intercostal bundles and posterior perichondrium with No. 0 chromic catgut, the pectoral sheath with interrupted No. 1 chronic catgut, the subcutaneous tissue with fine catgut and black silk for the skin.

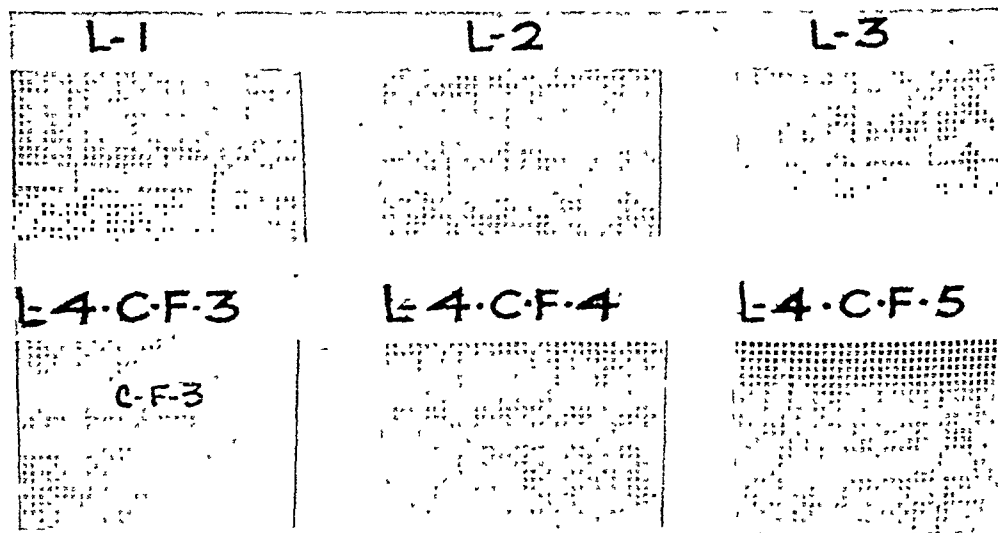


Fig. 3.—Sept. 27, 1943. Rate 80 per minute. Normal sinus rhythm. P-R interval 16 seconds; T_1 and T_2 are inverted and ST_1 is slightly convex upward. Tracing made twenty-four hours after episode characterized by chest pain, fever, leucocyte rise, and increase in sedimentation rate.

Postoperative Course.—Approximately ten hours after operation the patient complained of precordial pain and at that time a pulse irregularity was noted lasting several hours. For the first thirty-six hours there appeared a slight degree of cyanosis which was corrected by continuous oxygen therapy. For the next three days normal color was maintained by intermittent administration of oxygen. On the second postoperative day a small area of atelectasis developed in the right base posteriorly, clearing up on deep breathing, CO_2 and O_2 inhalations. On the eighth postoperative day a superficial wound infection was detected in spite of the fact that chemotherapy, which was instituted immediately after operation, had been administered in sufficient dosage to maintain a sulfadiazine blood level of 6 mg. per 100 c.c. Following adequate drainage the temperature, which had been elevated since the operation, returned to normal. On the ninth postoperative day a friction rub was noted in the right axilla unaccompanied by any discomfort or temperature elevation; this disappeared within the next forty-eight hours. On

the fourteenth day he was allowed to be up in a wheel chair and on the sixteenth day up and around the ward.

At the time of operation measures had been taken to combat disturbances of cardiac function and the following drugs placed at hand: Quinidine sulfate, 10 gr. in 100 c.c. of normal saline; calcium gluconate, 10 per cent solution for intravenous use; atropine sulfate, a 1:1000 solution of adrenalin hydrochloride and digitalis in solution for subcutaneous or intravenous administration. Happily, no evidence of rhythm disturbance or cardiac dysfunction of any character was encountered. Throughout the entire operation the pulse rate did not exceed 120 per minute, the rhythm remained regular, and the blood pressure ranged from 120 to 140 mm. of Hg systolic and from 72 to 90 mm. Hg diastolic. An electrocardiogram (Lead 2 only) (Fig. 4) was recorded at the time the foreign body was being removed from its bed and showed a normal sinoauricular rhythm and a rate of 120 per minute. Before leaving the operating room another tracing was made (Fig. 5) which showed an upright T_1 , and a T wave in Lead 4 that was inverted only 1 mm. During the remainder of his postoperative course the pulse rhythm remained regular except for the brief episode mentioned in the preceding paragraph; the blood pressure remained normal. No pericardial friction rub was ever detected and repeated x-ray and fluoroscopic studies showed no evidence of pericardial or pleural fluid. Electrocardiographic tracings were taken on the first, second, and fourth postoperative days and thereafter each week until the date of discharge Nov. 16, 1943. Samples of these tracings are shown in Figs. 6, 7, and 8, indicating only slight changes in the pattern of the T waves and S-T segments, but as a whole representing no evidence of improvement over the electrocardiographic tracings made prior to operation.

In other respects the operative results have been gratifying. There has been no recurrence of the shoulder and chest pain previously experienced and no cardiac arrhythmia detected other than that noted during the first twenty-four hours after operation.

At the time of discharge from the hospital, Nov. 16, 1943, to the Zone of Interior, the patient was walking freely about the hospital and surrounding grounds without discomfort. The operative wound was healed and firm without chest deformity. Movement of the thoracic cage was free and equal and the lung fields were clear to physical examination and x-ray study. A lateral view of the chest showed a slight thickening of the right anterior pleura. The temperature was 98.2; respiration, 18 per minute; pulse, 76 per minute; rhythm regular and the blood pressure 124/72. The apex was palpated in the fifth left intercostal space 8 cm. from the midsternal line. A grade 1 systolic murmur was noted over the pulmonic area and the pulmonic second sound was accentuated. There was no evidence of distention of the neck veins or ankle edema.

the upper anterior portion of the right ventricle. These adhesions were separated and a foreign body approximately 1 cm. in length was found encapsulated on the anterior aspect of the right auricle in close proximity to the superior vena cava. The fragment was very gently freed and removed. The pericardium was loosely approximated with interrupted sutures of No. 1 catgut. The incision in the thoracic wall was closed approximating the intercostal bundles and posterior perichondrium with No. 0 chromic catgut, the pectoral sheath with interrupted No. 1 chronic catgut, the subcutaneous tissue with fine catgut and black silk for the skin.

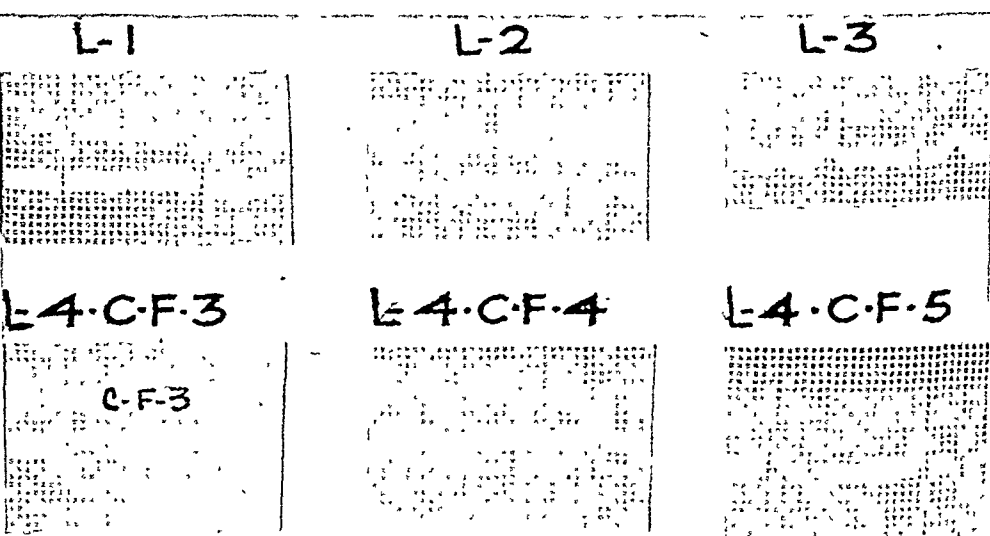


Fig. 3.—Sept. 27, 1943. Rate 80 per minute. Normal sinus rhythm. P-R interval 16 seconds; T_1 and T_4 are inverted and ST_1 is slightly convex upward. Tracing made twenty-four hours after episode characterized by chest pain, fever, leucocyte rise, and increase in sedimentation rate.

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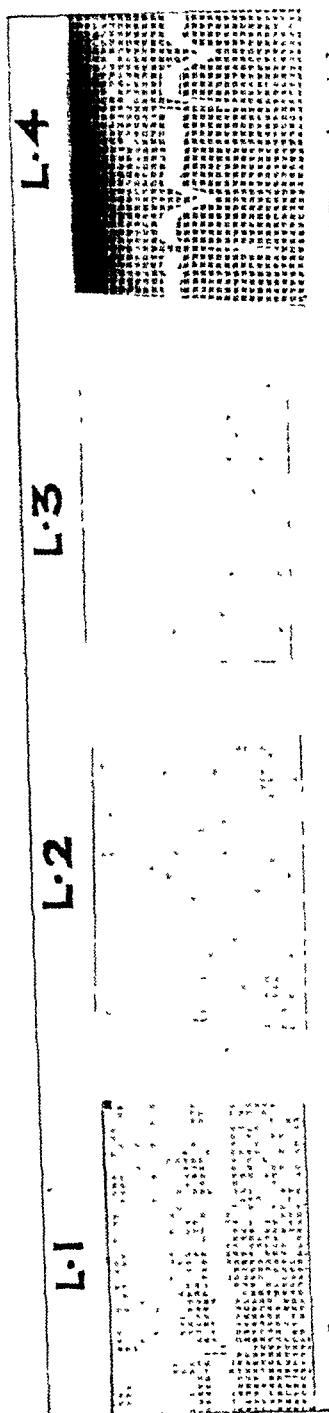


Fig. 7.—Oct. 11, 1943. Rate 90 per minute. Normal sinus rhythm. P-R interval 12 seconds; R₄ low; T₁ and T₄ are inverted.

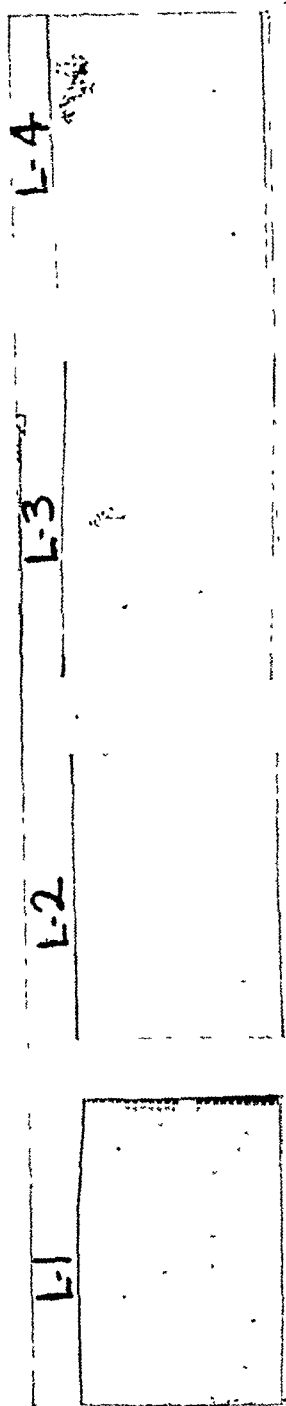


Fig. 8.—Nov. 15, 1943. Rate 80 per minute. Normal sinus rhythm. P-R interval 14 seconds; T₁ and T₄ inverted.

An electrocardiogram (Fig. 8) still showed inverted T waves in leads 1 and 4, with a normal sinus rhythm. The sedimentation rate was now 2.5 mm. per hour and blood and urine studies were normal.

SUMMARY

1. A case is reported of the successful removal of a metallic foreign body from the vicinity of the sinoauricular node producing adhesions between the anterior wall of the right auricle, superior vena cava, and pericardium, and extending downward over the right coronary sulcus onto the anterior wall of the right ventricle.

2. At the time of our first examination myocardial damage was present as indicated by recurrent attacks of precordial pain, cardiac arrhythmia, and inversion of the T waves in Leads 1 and 4 of the electrocardiogram.

3. There was no recurrence of the precordial pain and no further disturbance of rhythm was noted after the first postoperative day, in the period of seven weeks' postoperative observation.

4. No essential change was noted in the electrocardiographic tracings taken before and after operation.

The authors wish to express their gratitude to Lieutenant Colonel John P. Williams for his advice in the management of this case and to Captain George B. Craddock for the administration of the anesthetic.

REFERENCES

1. Horsley, J. Shelton, and Bigger, Isaac A.: *Operative Surgery*, St. Louis, 1940, The C. V. Mosby Company.
2. *Neuro Surgery and Thoracic Surgery*, Military Surgical Manuals, Vol. VI, Philadelphia, 1942, W. B. Saunders Company.

BONE REGENERATION FOLLOWING OSTEOMYELITIS

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THE processes of bone destruction and bone restoration in an osteomyelitis of the phalanges of a finger go on almost simultaneously. Nature's effort at restoration may seem to be delayed and its work is not instantly observable, but study of cellular destruction and restoration shows that they work harmoniously. Indeed, while the osteoclasts, regarded as destroying cells, are at work, they are preparing for the constructing cells, the osteoblasts, into which they change themselves when the time comes.

McLean and Bloom, for instance, observed that, "recovery (from bone necrosis) occurred by extensive intramembranous formation of new bone, accompanied by development of large numbers of active osteoblasts from the fibroblasts of the scar. These observations throw new light on the pathogenesis of experimental osteitis fibrosa which appears to develop, in part at least, as a reaction to the death or injury of the cellular elements of bone. Of more general biologic interest is the evidence that osteoblasts are not permanently differentiated cells, for they have been seen to change into phagocytes, osteoblasts, and fibroblasts; further fibroblasts have been seen to develop into osteoblasts which are then associated with the formation of new bone."

"The question," say Baetjer and Waters, "will present itself as to why in one case there is bone destruction and in the other bone production. The point of contact between the lesion and the bone is the point of stimulation. It takes nature some little time to lay down bone, so if the infection or lesion is virulent, the point of contact is swept away and a new one formed before there has been time for new bone formation; hence the process is entirely destructive. On the other hand, if the point of contact remains stationary for a short period, then nature has time to lay down new bone. So there are two well-defined changes taking place in bone, namely, destruction, indicating an advancing lesion, and production, indicating a lesion that is retrograding and is probably under control."

Wilensky says, "in bones, the seat of an osteomyelitic process, repair of the osseous tissue goes hand in hand with bone destruction," and Holman refers to the "almost infinite power of repair in bone, especially in infancy and early youth."

And, finally, Wilensky: "It is probable that all cells are formed into osteoblasts and can become osteoclasts. Just as osteoclasts originate from osteoblasts and their derivatives, they can again become osteoblasts and bone cells after their osteoclastic activity is over."

The foregoing statements are authoritative, theoretical, and perhaps observational descriptions in their application to the course of the osteomyelitis in the case under discussion. They are to be read in connection with the examination of the x-ray films, which tell as far as pictures can, the story of both the destructive and the restorative processes.

The patient in this case was a policeman who was bitten on the middle finger of his left hand by a man whom he was arresting. Striking another person on the teeth by accident would seem to be less risky than a deliberate bite, but even such accidental contacts are not an infrequent

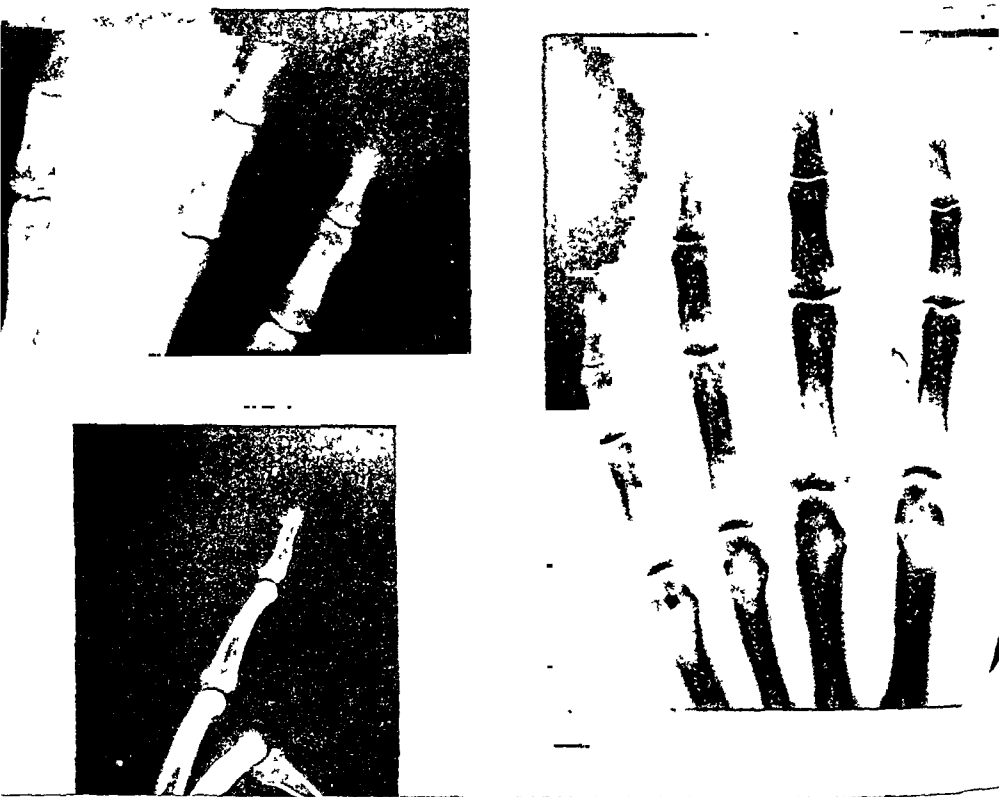


Fig. 1.—Sept. 5, 1938. This first roentgenogram was taken to determine whether a fracture resulted from a human bite near the end of the middle finger of the left hand. A human bite may develop a pressure as high as 300 pounds to the square inch. The finger was lacerated, red, sore, and swollen. No fractures were disclosed. Incision below the nail brought forth a copious, purulent discharge. Drainage was deemed adequate.

Sept. 9, 1938, four days later, it was thought that the infection was localized to the terminal phalanx. However, mouth organisms were numerous and virulent.

source of infection, and there have been cases in which a mixed anaerobic infection from organisms of the mouth resulted. The latter was true in this case. Pyogenic organisms, spirilla, and anaerobes were all present as the case progressed.

It is also to be noted that the patient in this case was 40 years of age, far beyond the age at which bone restoration is regarded as assured. Considering the extent of the destruction, the very marked soft tissue

involvement, and also the virulence of the infection, the bone restoration is the more interesting. And, finally, both the regenerative and the destructive processes are rather completely illustrated. Figs. 1 to 8 cover the entire period. Too often such a series is impossible because amputation offers an easier and speedier way to recovery.

A finger more or less is taken as a matter of consequence or inconsequence by the patient according to his occupation and economic condition. To a worker with pick and shovel such a loss might seem comparatively unimportant; to a piano virtuoso it would be vital. The patient in this case refused to permit the amputation, and so we have the x-ray films.

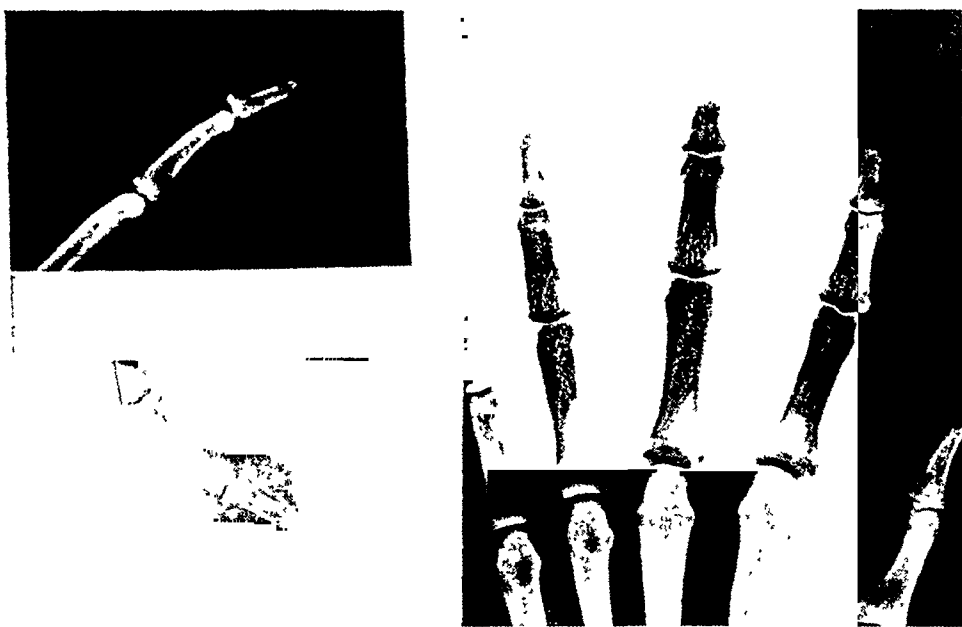


Fig. 2.—Sept. 16, 1938, six days later, while drainage was satisfactory, there developed a sloughing and necrosis around the nail. The nail was removed. Five days later osteomyelitis of the terminal phalanx was apparent. The destructive process was rapid. In the course of this infection, laboratory examination revealed staphylococci, spirilla, and anaerobes.

Beyond these, and for more particular information, reference is made to Knavel's text¹³ and to Auchincloss' chapter in *Nelson's Loose Leaf Surgery*.²

In dealing with any infection of the hand it is, of course, of first importance to have a thorough knowledge and understanding of the detailed anatomy of that very useful member. No part of the body, except the mental organ and the eye, is so much used or is so useful. The anatomy of the hand is complex and invites and deserves extended study. In the matter of hand infections, understanding of the principles of free drainage is particularly stressed by Kanavel. Auchincloss says that "early adequate drainage means early, comfortable convalescence. Delay means more necrosis, more dressings, osteomyelitis, in-

fection of the joint, and, if the lesion be near the distal flexion crease, a threatened tendon sheath."

The policeman was admitted to the hospital the morning after the wound was received. The following day the finger was incised below the nail, liberating a quantity of foul, purulent material. Drainage continued to be rather profuse for some time. The destructive process was advancing, as Figs. 1 to 7 show. Twelve days after the patient was admitted to the hospital the roentgenologist's report showed almost complete dissolution of the middle portion of the phalanx and tip with moderately advanced invasion of the distal three-fourths of the middle phalanx, and involving the distal joint; the soft tissues still showed considerable thickening.



Fig. 3.—Sept. 26, 1938, ten days later, the picture disclosed almost complete dissolution of the middle portion of the phalanx and tip, with moderately advanced invasion of the distal three-fourths of the middle phalanx. Subluxation of the terminal joint was practically complete. Sequestration of bone fragments was under way. The destructive process was receding in the usual way. The sequestration indicated the first effort at restoration of the destroyed bone.

Thus, it appears that the infection was advancing according to rule—from the distal anterior closed space by way of the nutrient foramen into the medullary cavity, with an osteomyelitis as the result. Thence the spread is to the flexor subtendinous space of the base of the distal phalanx and into the joint cavity, and so on to the middle phalanx with

probably entry to the tendon sheath. In the case under discussion there was involvement of (1) soft tissue, (2) bone, (3) joint, and (4) tendon.

The outcome of such a destructive and progressive osteomyelitis will depend on a number of things—the type of the organisms present, the age and condition of the patient, and, probably most important of all, the treatment.

The mixed infection, particularly one including anaerobes, is more serious than one involving a single organism. A child has a better chance to combat the infection and to obtain bone regeneration than an older person. The results in the case of the policeman, however, indicate that his age did not work against him. His recuperative power is one of the factors that give the case a lively interest.



Fig. 4—Sept 30, 1938, there was further invasion toward middle joint and increasing destruction of distal phalangeal bone. Sequestered fragments of bone were visible as evidence of the conflict between living and dead cells. Hot applications were discontinued.

The treatment covered the conventional range, and the conventional range is wide. The technique may change, but the principles are constant. Heat and cold, dryness and moisture, elevation and dependency, rest and activity, protection and massage, darkness and light, asepsis and germicides, pressure and its avoidance are all listed by Auchincloss, and "play their parts, and a host of other things besides "



Fig. 5.—Oct. 6, 1938, the osteomyelitis was progressing and the flexor tendons were undoubtedly involved. Edema was subsiding.



Fig. 6.—Oct. 10, 1938. Loose fragments of bone belonging to the distal phalanx marked the sequestration of the dead from the living cells. The sequestration level was the boundary line between the living and the dead cells and the point of conflict between them. If drainage is not complete, the living cells will be poisoned and die. In that case the work must be begun again at another joint by a new army of phagocytes, aided by a new incision for drainage. Note the extension into the middle phalanx.



Fig. 7—Nov 9, 1938. While the middle and proximal phalanges showed further invasion and the periosteum was stripped in the middle portion, there was visible improvement of the bone of the distal phalanx. At that point sequestration was completed and the bone was reorganizing its normal contour.



Fig. 8—Nov 16, 1938. This picture was taken after the hand had completely healed.

The final purpose of all treatment was to give the phagocytic type of cell a chance to work to the maximum advantage. All that promotes this, according to Auchincloss, is good; whatever hinders is bad. Indeed, if the welfare of the living cells, hard at work at the sequestration lines, be carefully attended to, much that was considered dead at one time would seem to be used in various ways as framework or even material with which the living cells reconstruct the part.

"Drainage," he says, "is perhaps the most subtle and important. Until sufficient time has elapsed for the sequestration bit of bone to be wholly separated through the action of living phagocytes, from the bone that yet lives—drainage plays a part."

If the drainage is not effective for any reason and the irritating discharges are blocked, they are thrown back on the living cells at work which are thus poisoned and die. The work of sequestering dead bone from living bone must then be carried on by a new army of cells farther along the bone, after another incision.

In the case under discussion, the drainage first established may have been imperfect, or the infection may have been particularly virulent, probably the latter. The destruction went on past the middle joint and into the middle phalanx, the distal joint was involved and the tendon sheath as well.

Five weeks after the wound was received, the finger was reoperated upon. Incision was made over the radial side from the midportion of the terminal phalanx to the mid-portion of the proximal phalanx. A small amount of necrotic tissue was removed. The flexor tendon was exposed and found to be destroyed distal to the proximal and middle phalanx. A posterior splint was applied.

As the authorities heretofore quoted have stated, it takes nature some time to lay down bone. The struggle of the living cells, however much help they may receive from the treatment, is not short and it is always desperate. In this case it seems that all the good as well as the bad factors were present and working. But it was four months after the removal of the tendon before the roentgenologist reported that much of the bone atrophy had disappeared. The osteomyelitis process had thoroughly abated and the cortex was commencing to be restored. The terminal joint, of course, was completely ankylosed.

The x-ray films enabled us to trace the course of the infection, resulting in a destructive progressive osteomyelitis, the beginning to the final elimination of the bone, and the resulting atrophy. The policeman patient, a valuable finger.

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REFERENCES

1. Arey, L. B.: *Developmental Anatomy*, Philadelphia, 1930, W. B. Saunders Company.
2. Auchincloss, Hugh: *The Surgery of the Hand*, in *Nelson's Loose Leaf Surgery*.
3. Baltzer, Frederick H., and Waters, Charles A.: *Injuries and Diseases of Bones and Joints*, New York, 1921, Paul B. Hoeber, Inc.
4. Bancroft, F. W.: Bone Repair Following Injury and Infection, *Arch. Surg.* 5: 646, 1922.
5. Bancroft, F. W.: The Fate of Necrosed Bone in Chronic Osteomyelitis, *Tr. Sect. Surg., General and Abdominal, A. M. A.*, pp. 154-165, 1922.
6. Best, Charles Herbert, and Taylor, Norman Burke: *The Physiologic Basis of Medical Practice*, Baltimore, 1939, Williams & Wilkins Company.
7. Brichel, A. C. J.: *Surgical Treatment of Infections of the Hand and Forearm*, St. Louis, 1939, The C. V. Mosby Company.
8. Cowdry, E. V.: *Textbook of Histology*, Philadelphia, 1938, Lea & Febiger.
9. Gray, Henry: *Anatomy of the Human Body*, edited by Warren H. Lewis, Philadelphia, 1936, Lea & Febiger.
10. Harris, H. A.: *Bone Growth in Health and Disease*, London, 1933, Oxford University Press.
11. Holmes and Ruggles: *Roentgen Interpretation*, Philadelphia and New York, 1926, Lea & Febiger.
12. Jackson, Morris: *Human Anatomy*, Philadelphia, 1933, The Blakiston Company.
13. Kanavel, Allen B.: *Infections of the Hand*, Philadelphia and New York, 1925, Lea & Febiger.
14. Leriche, R., and Polcard, A.: *The Normal and Pathological Physiology of Bone*, St. Louis, 1928, The C. V. Mosby Company.
15. Levander, Gustav: A Study of Bone Regeneration, *Surg., Gynec. & Obst.* 67: 705, 1938.
16. Maximow and Bloom: *Textbook of Histology*, Philadelphia & London, 1935, W. B. Saunders Company.
17. McLean, Franklin C., and Bloom, William: *Mode of Action of Parathyroid Extract on Bone*, Science, 1937.
18. Wiggers, Carl J.: *Physiology in Health and Disease*.
19. Wilensky, Abraham O.: *Osteomyelitis, Its Pathogenesis, Symptomatology, and Treatment*, New York, 1934, The Macmillan Company.

A PRACTICAL CONVERSION OF FLAGG TYPE LARYNGOSCOPES

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IINTRATRACHEAL anesthesia, properly applied, offers such rewards in safety and convenience, particularly in operations about the head and in chest surgery, that it should be in use in all hospitals. Moreover, there are emergencies which call for the accurate aspiration of inhaled vomitus, or occasionally for the removal of foreign bodies above the level of the glottis, in which delay while a specialist is being sought might prove serious. Those who have seen the dramatic relief afforded by tracheal aspiration to patients who are too weak to raise the secretions that are suffocating them, and likewise those who are aware of how frequently the battle is lost because of that most subtle of killers, chronic anoxia, will avail themselves as far as possible of the positive and simple direct-vision technique of laryngoscopy.

The purpose of this communication is to call attention to some points of practical importance to those undertaking laryngoscopy as it assumes its rightful place in general medical and surgical practice. The first point is of the greatest importance—to emphasize that the neck of the patient should be strongly flexed on the chest and relaxed instead of being extended as the beginner usually assumes. The head itself may then be extended (bent backward) upon the neck at the atlanto-occipital level as much as is possible with the neck thus flexed upon the chest.

There is usually no difficulty in passing the laryngoscope blade to raise the back of the tongue (as the patient lies supine with head toward operator) and in exposing the epiglottis, although the overly anxious may fail to get oriented squarely by hurrying over the landmarks. The blade is then withdrawn slightly to scoop under the tip of the epiglottis and lift it forward. If the laryngoscope is entered too far it overrides the slanting glottis and enters the esophagus, yet if it is withdrawn too far the tip of the epiglottis is released and flips back down over the glottis. Lateral deviation gives entry to the pyriform fossae, which may be mistaken for the glottic chink. All this, plus the necessity for firm and constant lifting, may make control difficult. The laryngologist, using the beautifully balanced Jackson instrument, has minimal difficulty because his instrument is C shaped and he uses the horizontal handle bar not only to lift directly but as a lever to control deviation.

However, there is a definite place for the self-contained laryngoscope. Flagg¹ recognized that, for intubation and for emergency work, a laryngoscope was needed with a large lumen, open along one side to permit ready disengagement of tubes or instruments, and that it should be

Aided by a grant from the Comly Fund for Research.
Received for publication, Sept. 26, 1944.

self-contained, ready for instant use and control. He eliminated the dangling cords and battery box by placing flashlight batteries within the handle, developing the pattern now so widely used under his name. Difficulty is noted, particularly by the novice, because of the lack of a horizontal member for the handle bar. This forces the hand to apply a twisting stress to the vertical handle, and even with a strong wrist there results marked loss of delicacy of control. There is also a common tendency to *pry*, using the upper teeth as a fulcrum, which may cause pain or damage even though an attempt is made to provide a shield for the teeth. It must be realized that particularly in intubation and in individuals with thick short necks, considerable force must be applied to the tissues behind the hyoid bone to obtain adequate exposure, sometimes enough to lift the patient's head from the table. If done correctly there is no danger of local trauma as the parts shift together to the required alignment. The point is that the load lies largely on the tip of the blade.

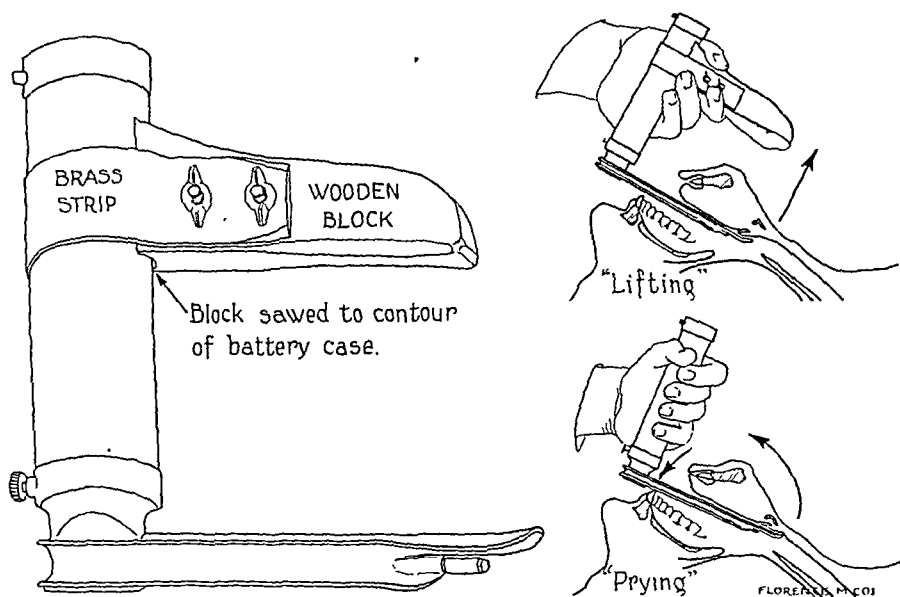


Fig. 1.—Flagg pattern laryngoscope, showing proper use to lift rather than to pry.

An adjustable wooden handle was therefore added to the usual Flagg laryngoscope used for intubation. (See Fig. 1.) In thoracic operations performed during the past year at the University Hospital, members of the cooperating research surgery and anesthesia departments found their work greatly facilitated by this simple addition. Since then I have seen the excellent laryngoscope developed by Dr. U. H. Eversole, in use at the Lahey Clinic. This is operated by small batteries in the handle but is much nearer in proportions to the Jackson type than are the Flagg models. It is C shaped (provided with a horizontal member

for the handle). Although it is not described in the literature it is available commercially. It is felt that this note is warranted, however, by the number of Flagg type laryngoscopes already distributed whose usefulness could be readily increased by adding such a handle to facilitate their proper use. It is of interest to note that in some modifications of the basic Flagg design the vertical handle has been angled toward the blade in an attempt to secure this more favorable leverage and control.

MacIntosh² has recently described a model which has an upcurved blade, to be passed to the base of the tongue and to lift from this point without engaging the epiglottis, but after brief trial I find the merits of this clever simplification of the technique open to question. Wiggin proposes still another modification of the blade for intubation by flaring the side. The appearance of these reports suggests the further room for improvements in the basic Flagg design, but in some form his valuable contribution should be used more extensively. The full techniques are ably discussed in the readable and authoritative books by the Jacksons,⁴ and Flagg.⁵

REFERENCES

1. Flagg, P. J.: The Exposure and Illumination of the Pharynx and Larynx by the General Practitioner; A New Laryngoscope Designed to Simplify the Technic, *Arch. Otolaryng.* 8: 716, 1928.
2. MacIntosh, R. R.: New Laryngoscope, *Lancet* 1: 205, 1943.
3. Wiggin, S. C.: A New Modification of the Conventional Laryngoscope and Technic for Laryngoscopy, *Anesthesiology* 5: 61, 1944.
4. Jackson, C., and Jackson, C. L.: *Bronchoscopy, Esophagoscopy and Gastroscopy*, Ed. 3, Philadelphia, 1934, W. B. Saunders Company.
5. Flagg, P. J.: *The Art of Anesthesia*, Ed. 6, Philadelphia, 1939, J. B. Lippincott Company.

SURGERY

VOL. 17

APRIL, 1945

No. 4

Original Communications

ACUTE PANCREATITIS

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PREVIOUS to 1938 the diagnosis of acute pancreatitis was, at best, uncertain. It was a diagnosis made from the clinical picture of an acute abdominal emergency, often alarming in its intensity, and supposedly calling for urgent surgery. The diagnosis was likely if severe epigastric pain struck suddenly in a middle-aged obese individual. If this was accompanied by vomiting, shock, tenderness in the epigastrium verging toward the left, absence of fever, a relatively rapid pulse, and a high white blood count, the diagnosis became more certain. Transverse radiation of pain across the upper abdomen, increasing distention, and tenderness in the left costovertebral angle would give additional support. Attempts would be made to rule out perforated peptic ulcer by x-ray examination; acute biliary tract disease, jaundice often being present; intestinal obstruction or mesenteric thrombosis; coronary occlusion by electrocardiographic examination; and peritonitis. When everything had been done, the attendants would be oftentimes in a dilemma. Operation would be advised to resolve the anxiety and to avoid missing an acute surgical condition.

What was needed at this time was a dependable, easily performed laboratory test. This test would of necessity be one which could be done without elaborate apparatus as it would have to be done at any time, day or night. And it would have to be a test which could be finished quickly. Somogyi^{31a} gave us such a test. Other tests which had been in use, such as the Wohlgemuth test (starch splitting), did not permit measurement of small changes and were too time consuming. The viscosity of starch paste under action of diastase was variable and inadequate (Somogyi^{31b} and Polowe²⁵). The serum lipase test required a twenty-four-hour wait and was elevated in pancreatic cancer as well

Read at a meeting of the Nashville Surgical Society, Jan. 12, 1945.
Received for publication, Jan. 26, 1945.

as in pancreatitis (Johnson and Boekus). Polowe's cuprous oxide precipitation demanded thirty minutes' incubation, then centrifuging, etc.

Somogyi's rapid method (amylolastic activity) is a quantitative measurement of the *reaction time* and not of the reducing power of the reaction products. The results obtained by this procedure are computable in terms of reducing power and identical with such reductions. This permits estimation of low values and accuracy in high ranges (Somogyi^{31a}). The test can be reported in twenty minutes. The blood amylase content in healthy persons is maintained at fairly constant levels. Eighty per cent of healthy ambulatory adults have levels between 80 and 150; the remainder have a low range of 60 to 80, or a high range of 150 to 180. Blood amylase values below 60 and above 200 are considered abnormal. The origin of the diastase content in the normal blood is at present unknown. It is completely absent in the newborn infant; appears at 2 months, is measurable at 3 months, and reaches normal at 1 year. It is not influenced afterward by age, sex, amount or type of food, fasting, dehydration, diuresis, exercise, or sleep. Under normal conditions neither the pancreas, salivary glands, nor liver contributes to the blood diastase level. Acute pathologic changes in the pancreas or salivary glands may cause a temporary effusion from these glands into the blood stream. This causes an increase in the diastase (amylase) content of the blood. The increase takes place quickly, reaches a high level and gradually subsides to normal within a few days.^{21-23b} Injury to the pancreas tends to increase the amylase activity; injury to the kidney or to the liver decreases it (Polowe²⁵). The serum amylase can be useful in differentiating perforated peptic ulcer from pancreatitis and also in determining the site of perforation according to Probst and his co-workers.²⁷ When the serum amylase reading is low or subnormal in sharp epigastric pain it rules out acute pancreatitis or perforating ulcer into the pancreas; very high readings indicate acute pancreatitis; moderate elevations may mean perforation into the pancreas. Aspirated fluid from the peritoneal cavity can be tested for amylase activity in a doubtful case. In acute pancreatitis the peritoneal exudate gives high readings.

Etiology.—The fundamental cause for the behavior of the pancreatic ferments in pancreatitis still remains in debate. There is no question that living tissue is not affected by the pancreatic enzymes. Whipple and Goodpasture³² demonstrated that the pancreatic juice was harmless intraperitoneally and intravenously. Biopsy and operations on the pancreas are not followed by pancreatic necrosis. When bile is injected into the pancreatic duct, pancreatic necrosis may occur. This is because of the local cytolytic and destructive properties of bile salts and not because of activation of intraductal trypsinogen. Active trypsin is incapable of digesting living tissue; it acts as a catalyst in facilitating the hydrolysis of proteins by the alkali of the pancreatic juice. The locally

destructive action of pancreatic juice is dependent on the concentration of the alkali. Infection of the injected bile augments the destructive action. The toxic effect is neutralized by proteins of the blood serum. Hemorrhage is probably a protective mechanism (Gaither¹²). Jones¹⁸ does not agree with this. The pancreatic ducts which are not obstructed remain unharmed but anything which partially or completely blocks the ducts may cause acute pancreatitis. There are five principal contributing causes: (1) trauma, accidental or surgical, (2) infections with extension to the pancreas, biliary tract, duodenal ulcer, etc., (3) toxic, alcohol, drugs (arsphenamine), anesthesia, (4) obstructions to biliary tract, stone, spasm, infection, tumor, duodenal diverticulum, *Ascaris*, and (5) circulatory factors, stasis, hypertensive apoplexy, thrombosis, and embolism.

Dragstedt and his associates claimed that 60 per cent of acute pancreatitis arises in patients with antecedent biliary tract disease. In our series the figure was 62 per cent. In 10 per cent of these cases there is the common channel of Opie. The rest of the cases have spasm of the sphincter of Oddi as described by Archibald (Jones¹⁸). Lynch²⁰ found duct obstruction the main etiologic event, although vascular occlusion and infection caused a considerable proportion of the acute disease. Gaskell¹³ claims that there is a form of acute necrosis of the pancreas as a cause of sudden death. Trauma of the head of the pancreas can produce this result. He cites ten cases with post-mortem examinations to support his views. Smyth³⁰ believes the vascular factors to be important and demonstrated all the pictures of acute pancreatitis following mercury injections into the arterial supply of the pancreas of dogs. Ackerman¹ reported a fatal case of acute hemorrhagic pancreatitis following transfusion of mismatched blood. Severe instances of acute disease following heavy drinking bouts have been noted by several authors. We have seen a number of such instances. Ogilvie²⁴ reported three cases of pancreatic necrosis associated with duodenal diverticula, thus favoring an obstructive etiology. Allergy has been implicated by Brodie and Ficarra.³

Pathology.—There are at least two types of acute pancreatitis. The more common form is acute pancreatic edema, called by Elman interstitial pancreatitis. This manifests itself by a boggy swollen pancreas with fluid under tension and is accompanied by fat necrosis in a large proportion of cases. The disease does not progress to hemorrhage and necrosis but subsides spontaneously in most instances if not disturbed.

The other type is hemorrhagic necrosis. This is a serious disease with death of a large part of the organ.

Sequelae.—As sequelae to these forms we may have acute pancreatic abscess, an immediate or late result of autolyzed infected necrotic tissue, or pseudocyst of the pancreas where the above necrotic tissue is walled off and the infection has burned out.

The acute edematous pancreatitis is followed by chronic inflammation in a large percentage of cases. When the disease has subsided and the patient is explored later, a hard enlarged pancreas is frequently encountered. Experimentally, Ireneus¹⁶ has showed that the acinar cells tend to recover and become functionally efficient in about four weeks in experimental animals. Residual changes consist of interlobar and inter-acinar fibrosis, lymphocytic infiltration, and edema.

Glycosuria is noted in about 11 per cent of acute pancreatitis cases. Shumacker²⁹ claims that at least 2 per cent of all patients with severe acute pancreatitis develop diabetes; and of those surviving 3 to 10 per cent will develop it in time. Systematic follow-up studies should be made.

Diagnosis.—The symptoms are too well known to demand comment. Suffice it to say that acute pancreatitis can be diagnosed only rarely without the special amylase test, nor can the acute edematous form be differentiated from pancreatic necrosis at the beginning of the attack. Severe pain, vomiting, constipation, distention, and tenderness are common to many conditions in the abdomen and chest. Even the electrocardiogram may show changes suggestive of myocardial infarction or coronary thrombosis. The triad of upper abdominal peritoneal irritation, elevated serum amylase test, and electrocardiographic changes should establish the diagnosis of acute pancreatitis (Gottesman and co-workers.¹⁴). Perforated peptic ulcer, coronary disease, tabetic crises, peritonitis, severe biliary tract disease, acute intestinal obstruction, mesenteric thrombosis, and ectopic pregnancy must all be considered in differential diagnosis. By the course in the hospital it should be possible to separate the pancreatic edema from pancreatic necrosis. The former usually gives history of previous attacks, less prostration at the onset, and a high amylase reading. Over the course of three to five days the attack subsides spontaneously with return to normal. Pancreatic necrosis on the other hand is almost always prostrating at the start; the amylase test may or may not be elevated; the patient fails to improve during the conservative treatment (Casberg⁶ and Elman^{10b}); and if nothing is done, he dies or goes through a prolonged illness with sequelae such as abscess or cyst formation.

There may be repeated attacks of acute pancreatitis. Four of our patients had secondary attacks while in the hospital after the first attack had subsided. Two had second acute attacks within one year, and one patient had three separate acute attacks within a period of two years.

Treatment.—In acute edematous pancreatitis, diagnosed by amylase test, the curve should be followed and treatment should be conservative. Immediate operation is contraindicated. After the acute disease has subsided, the gall bladder should be studied and interval operation

carried out. The passage of small gallstones is frequently the cause of an acute attack of pancreatitis. In one of our patients a small stone was vomited during the height of a pancreatitis attack with prompt amelioration and recovery. Certainly in any of these patients with biliary tract disease there is a rationale for exploring the common duct and dilating the lower end to abolish sphincter spasm. Some surgeons

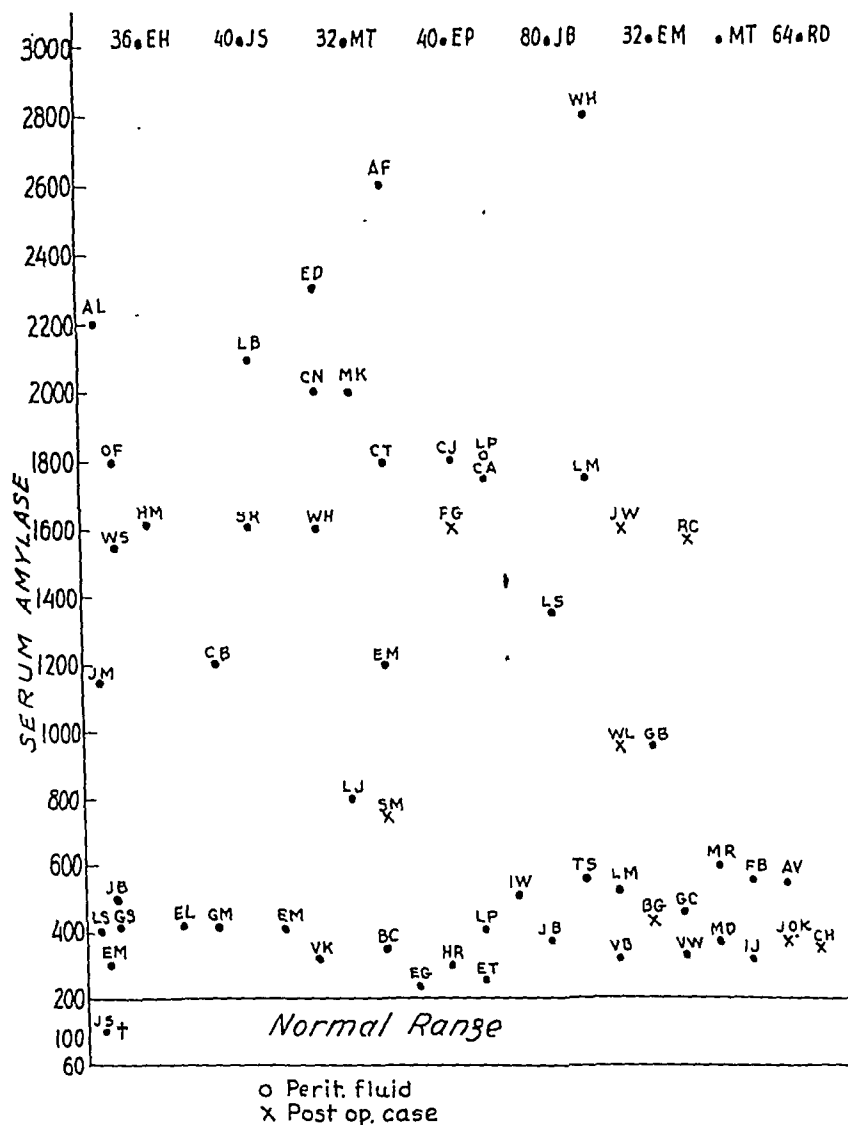


Fig. 1.—Acute pancreatitis gives serum amylase above the normal range except late in the onset and after the pancreas is necrotic.

advocate drainage of the common duct for three to four weeks but this, to my mind, would depend on the amount of infection present. If the bile is clear, I do not hesitate to close the common duct without drainage. All cases of pancreatic necrosis demand operation as soon as the

diagnosis can be established and the patient brought into condition for it. The necrotic tissue should be given a chance to extrude itself along a drainage tract, either through the peritoneal surfaces above or below the stomach or by drainage through the foramen of Winslow. If the

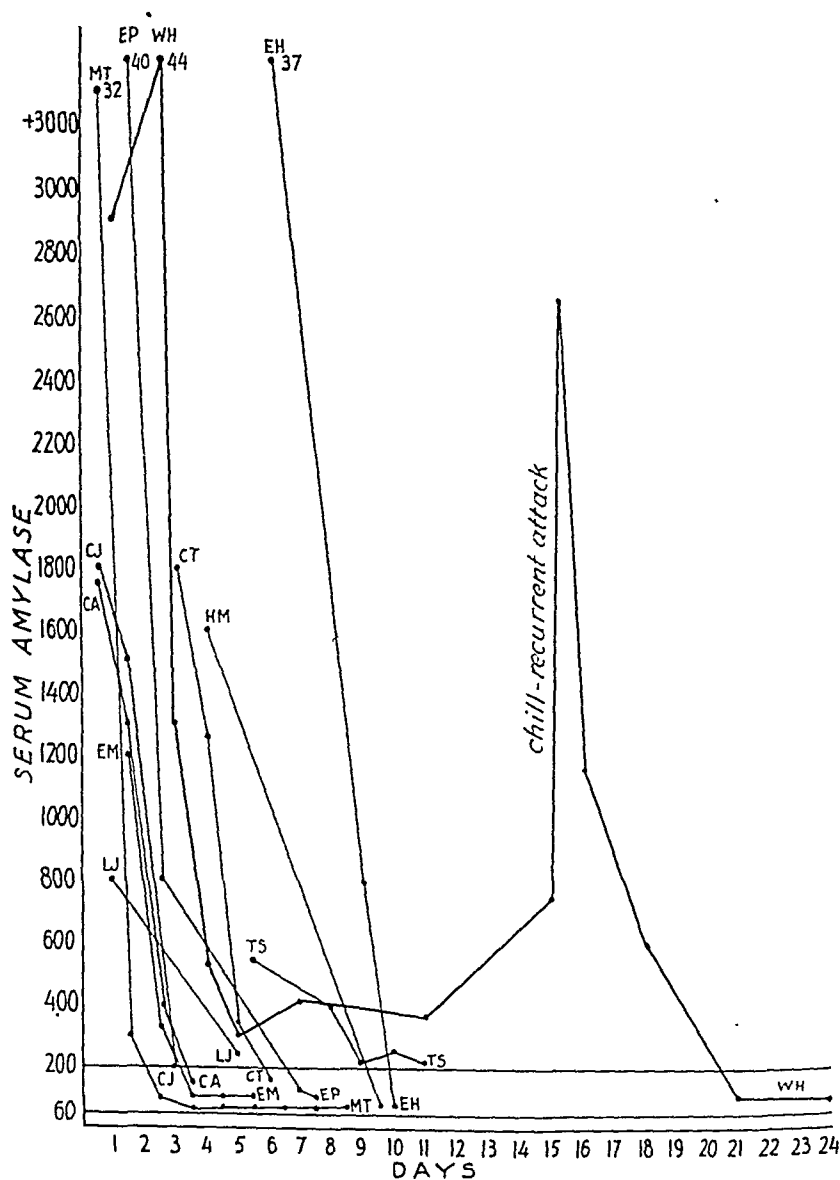


Fig. 2.—The serum amylase drops to the normal range within four to five days in most instances of acute pancreatic edema. In one patient a recurrence of an acute attack came before a drop to the normal range.

common duct is blocked it also should be drained. A certain number will be saved in this manner.

For the relief of intractable pain during the attack the opiates may be successful. Nitroglycerin at times relaxes the sphincter of Oddi

TABLE I

	DIED	PER CENT
<i>Acute Pancreatic Edema</i>		
70 Cases	11	15.71
41 Cases with operation	11	26.82
29 Cases without operation	0	0.00
<i>Acute Pancreatic Necrosis</i>		
27 Cases	19	70.37
18 Cases with operation	10	55.55
9 Cases without operation	9	100.00

and gives dramatic relief (Elman^{10a}). Paravertebral injection in the eighth to tenth dorsal segments has been advocated (Popper^{26a} and Dinsmore and Nosik⁹).

Large meals and alcoholic bouts should be avoided in the period after leaving the hospital. In some cases mild pancreatitis attacks come on even after biliary tract surgery in these patients. Elman^{10a} gives his patients tablets of $\frac{1}{400}$ gr. (0.0006 Gm.) glyceryltrinitrate to carry with them. If one of these tablets is put under the tongue promptly at the beginning of an attack it may be prevented.

Results.—Review of the current literature shows that any large series of acute pancreatitis cases carries a considerable mortality. Thus, Fallis¹¹ had 46.2 per cent, Brütt⁴ 50.0 per cent, Morley²² 35.3 per cent, Yates²² 50.0 per cent, Ogilvie²² 50.0 per cent, Griessmann¹⁵ 34.0 per cent, Carter and Hotz⁵ 53.3 per cent, Connell⁸ 36.3 per cent. Lampson¹⁹ 33.0 per cent, and Reichl²⁸ 46.23 per cent, an average of 43.43 per cent for these reports. In our previous collected results for immediate operation out of 911 cases, there were 447 deaths or a mortality rate of 49.06 per cent.^{23a} The combined figures show only a slight improvement, 46.24 per cent. Our own figures show 67 cases in which operation was done, with 24 deaths, or 35.8 per cent.

As long as surgeons operate without using the amylase test to help in their diagnosis, there will be a mortality from acute edematous pancreatitis. This should not be, but it accounted for two deaths in our series of 19 cases after the amylase test was available. Previous to that our mortality was 9 out of 22 cases in this group when operation was necessary to decide what type of disease we were dealing with. When

TABLE II

	DIED	PER CENT
<i>Acute Pancreatic Abscess</i>		
11 Cases	6	54.54
8 Cases with operation	3	37.50
3 Cases without operation	3	100.00
<i>Postoperative Pancreatitis</i>		
20 Cases*	15	75.00

*Before 1939, post mortem was the only way to know, therefore others may have had it; now it can be tested.

the test was used properly we treated 29 cases of pancreatic edema without a death, not operating during the height of the reaction.

CASE REPORTS

R. D. (Hospital No. 217849), a 52 year old well developed and well nourished man was admitted to the hospital, being referred by his doctor, with a diagnosis of perforated gastric ulcer. He was seen in the emergency department by numerous observers who all agreed on the diagnosis. His history was as follows: Fourteen hours previous to admission he was awakened by epigastric pain. Three hours before it became much worse, with radiation to his back. The pain was relieved by morphine. He had a vague gastrointestinal history previously; taking soda had brought relief. On entering, his temperature was 36.5° C., pulse 82, respiration 24, blood pressure 130/90, white blood cells 11,000. His abdomen was flat. There was boardlike spasm in the upper quadrants and spasm in the flank on the right. No peristalsis was seen. Flat plate of the abdomen showed no free air. I was asked to see him before I went home and agreed with the diagnosis. I asked that the operating room be set up in preparation for a perforated ulcer operation, but I suggested that an amylase test be done just as a matter of interest. By the time I reached home there was a telephone message saying that his amylase test was 6,400. Needless to say, operation was not performed. The next day his amylase was 2,100; it gradually subsided over the next week and he went home following this against advice, because he was a farmer who wanted to get his crops in and he would not stay for study, gall bladder series, etc.

S. R. (Hospital No. 178017) was a tremendously corpulent, 39 year old woman who had had recurrent attacks of gall bladder disease. Twelve days before admission she had a severe attack associated with dull pain, nausea, and vomiting. Morphine and atropine failed to relieve her. She had right upper quadrant tenderness and spasm in the gall bladder area. Blood count was 32,000, icterus index 18, and blood amylase 1,600.

The attending surgeon thought that she was in urgent need of operation, the diagnosis being cholelithiasis, stone in common duct. Cholecystectomy with choledochotomy was done on the day of admission. The patient died two days after operation. At operation she had marked edema of the pancreas as well as gall bladder infection.

S. K. (Hospital No. 183524), a 65 year old well nourished man, was on the medical service, being studied because of right upper quadrant pain. Gastrointestinal series showed duodenal ulcer, and gall bladder test showed poorly functioning gall bladder. While still in the hospital he had a sudden onset of acute, persistent, severe, pain and spasm, vomiting, marked tenderness in the upper abdomen, most marked in the epigastrium. His abdomen was rigid, less so in the lower than in the upper. Liver dullness was present. There was rebound tenderness in the epigastrium. Temperature was 38° C., pulse 130, white blood count went from 12 to 16,000. Blood pressure was 190/85. No flat plate of the abdomen was taken for free air but a diagnosis was made by three surgeons, who saw this patient, of perforated duodenal ulcer. He was taken to the operating room and under vinethene and ether, free fluid and swelling of the entire pancreas with edema were noted. The abdomen was closed. The patient died the second day following operation.

Post mortem examination showed acute pancreatitis with fat necrosis and peritonitis. From the fluid removed at operation amylase test showed a reading of 1,070.

E. M. (Hospital No. 134723), a very obese bartender, 34 years old, and a chronic alcoholic, was admitted to the hospital for the sixth time with a diagnosis of chronic cholecystitis, stones, and nephritis. He had continued attacks of nonradiating

epigastric pain, nausea, and vomiting. Three days before admission these attacks were unusually severe in the right upper quadrant with epigastric pain and constant cramps, accompanied by vomiting. There was no relief from opiates. Temperature was 37.6° C., pulse 100, respiration 30, blood pressure 200/115. He was a tremendously obese man. There was acute tenderness in the epigastrium, but also in the lateral wall, especially over the gall bladder. His liver was three to four fingerbreadths below the costal margin. White blood count was 16,600, icterus index 13. He continued to have pain with no relief, and repeated vomiting. He called out in pain and drank a large amount of water. He went into shock, became unconscious. Medical men considered this to be a case of diffuse peritonitis with empyema of the gall bladder. Surgical consultation was called. It was suggested that pancreatitis might be a possible diagnosis. Accordingly, he was tapped. Blood-tinged fluid was obtained which gave an amylase reading of 400. That night he vomited and aspirated the vomitus and died.

Post-mortem examination showed acute pancreatitis, aspiration pneumonia, chronic cholecystitis, and cholelithiasis.

M. K. (Hospital No. 161450), a slightly obese, 22-year-old woman, had some pork chops for dinner. Twenty-four hours later she had severe epigastric pain radiating to the back, low down. It was agonizing and boring in character. She was nauseated but did not vomit. She was in acute distress, rocking back and forth in pain, her arms pressed to her back. There was a boardlike spasm of the whole abdomen and marked tenderness over the gall bladder. There was slight distention and some spasm to the left. Murphy's sign was positive. Temperature was 37.6° C., pulse 84, respiration 20, white blood count 17,000, amylase 2,000. She was given 75 r. units of x-ray treatment. During the night she vomited a small gallstone. The next day she felt much better. Her amylase test twenty-six hours later was 230. Five days after this, cholecystectomy with exploration of the common duct was done. The gall bladder showed chronic cholecystitis with one small stone. There were no stones in the common duct. She was discharged well.

L. B. (Hospital No. 2361), a very obese, 49-year-old woman, was admitted to this hospital previously in August, 1932, with a history of nausea and vomiting. In October, 1932, she had nausea and vomiting, dizziness, and dull pain in the upper abdomen. This was increased during vomiting. There was general abdominal pain and tenderness, more in the right flank, slightly more in her epigastrium. Temperature was 38.8° C., pulse 108, respiration 24, blood pressure 126/80. A diagnosis of acute pancreatitis was made. Exploration was carried out. Stones were found in the gall bladder. The pancreas was indurated and there was an abundance of fluid. Cholecystostomy was done.

The patient was near death following operation, but after twelve hours she made a rapid improvement and the tube drained for forty-five days, after which she was discharged. She was to come back for cholecystectomy later the same year. An appointment was made for Nov. 20, 1932. She did not appear at this time, however, and she felt well. She continued working as a school nurse. Nine days previous to this admission, June 12, 1940, she had an upper respiratory infection and three days before, crampy, abdominal pain, and much gas on the stomach, relieved by enema and vomiting. Temperature was 37.6° C., pulse 85, respiration 18, blood pressure 115/88. She was apparently in no distress. There was a subsiding pharyngitis. Abdomen was soft with no spasm. There was a slight resistance to deep palpation on the right of the upper abdomen. White blood count was 16,000. Flat plate of her abdomen showed nothing. Amylase test was 2,100. Oral cholecystogram showed no gall bladder shadow. She was given intravenous fluids and felt much improved; in the course of three days the condition subsided to normal. She was discharged without operation although it should be carried out, I believe. This is a good case because it is a two-times proved acute pancreatitis.

L. P. (Hospital No. 27793), a 25-year-old, obese Negro woman, was admitted to the hospital April 1, 1942. Two hours before she had severe crampy abdominal pain associated with nausea and vomiting. Two weeks before she had crampy abdominal pain associated with her periods, which was usual. Her two last periods had been of unusual length, eight to nineteen days instead of the usual three to four days.

Two hours before she had severe crampy abdominal pain, nausea, and vomiting without radiation of the pain, although some of it was in her left shoulder. Temperature was 37.4° C., pulse 72, respiration 18, blood pressure 110/60. She did not seem to be in any very acute distress. There was marked tenderness to deep palpation in the epigastrium but no distention or spasm. There was a mass in the right side close to the uterus and the white count was 32,000. The diagnoses suggested were many: cholecystitis, penetrating peptic ulcer, ruptured ectopic pregnancy, ruptured follicle, hemoperitoneum, and acute pancreatitis. Acute pancreatitis was diagnosed by the fact that her amylase registered 400 and a cul-de-sac puncture was made which gave 2,500 c.c. of bloodstained fluid. Amylase on this was 1,800. Flat plate of her abdomen showed gallstone shadow, probably.

For one week she was treated by small doses of radiation therapy and her amylase dropped to the lower limits of normal. On April 14 it was decided that she had a left subphrenic abscess and this was drained, the pus pocket being identified. Fat necrosis was demonstrated in the tissue and necrotic fat from the drainage area. She was placed on Wangenstein suction. Intravenous fluids were given and she had a stormy course, draining profusely and developing glycosuria. She was given sulfonamide drugs and the condition gradually cleared up; on June 29 the wound was closed and there were no complaints. We have not been able to contact her since she left the hospital.

E. M. (Hospital No. 82365), a 53-year-old well-developed and well-nourished woman, was admitted to the hospital May 16, 1943. Twenty-four hours previously she had a sudden onset of very severe mid-abdominal pain over the gall bladder, radiating to the back, shoulders, and around to both sides. She vomited repeatedly. At entry she was very ill and pale and had general tenderness with spasm, increased in the right upper quadrant and epigastrium. There was rebound and referred tenderness in the right upper quadrant. Temperature was 37° C., pulse 108, respiration 24, and blood pressure 105/50. Icterus index was 8, blood amylase 3,200.

In 1912 her gall bladder had been drained and she had many attacks of No. 3 pneumococcus infections from that time on. A diagnosis of acute pancreatitis and chronic cholecystitis and cholelithiasis was made. Her amylase subsided over the next week so that it was within normal range. On May 31 a cholecystectomy with drainage and dilatation of the common duct was carried out. A fibrous constriction of the common duct was found. There were no stones in it, although the gall bladder contained three. The common duct was drained with a catheter which was taken out June 5, 1943.

The patient has remained well following this.

E. O. (Hospital No. 164872) was admitted to the emergency department May 6, 1940. While in church the day before, this 49-year-old woman had sudden pain in the right upper quadrant just below the costal margin. The pain became more severe that evening and radiated strongly to her back. She had fever and chills. The pain was constant, was not relieved by induced vomiting, but was somewhat relieved by hypodermic injection. On entry her temperature was 40° C., pulse 104, respiration 24, and white blood count 23,400. She was acutely ill, pale, and slightly jaundiced. Her extremities were cold and sweaty. There was deep tenderness in the right upper quadrant and none elsewhere. Her urine showed positive bile. Amylase was 50 on admission, icterus index 15. After two comfortable nights she

had severe epigastric pain and distention and boardlike spasms in both upper quadrants. There was marked tenderness in the right upper quadrant, some in the left upper quadrant, but no radiation. Her vital signs were up again. This time amylase reached 1,800 and the icterus index was 27. Her left pupil had been dilated since admission and was noted to be so still. The next day amylase was 2,300 and the icterus index 30. She was given radiation treatment consisting of two doses of 100 r. and 75 r. each and there was immediate subsidence of the amylase reaction down to 200 by noon of May 10. The icterus index dropped to 10. On admission her diagnosis had been a question of pneumonia or of acute cholecystitis, but the positive amylase test when she had the attack in the hospital made it apparent that we were dealing with an acute pancreatitis. After hydration and transfusion she made a marked clinical improvement and nine days after admission cholecystectomy was done with drainage of the common duct. The gall bladder showed acute and chronic cholecystitis without stones. The pancreas gave evidence of acute pancreatitis. It was enlarged to twice its normal size, firm, edematous, and had a bilious discoloration to it. Convalescence was uneventful and she was discharged on the fourteenth day. There was no follow-up study.

E. P. (Hospital No. 177924) was admitted to the emergency department May 14, 1941. She was a 48-year-old woman who had a sudden onset of severe epigastric and right upper quadrant pain. The pain radiated to the left and through to her back with some pain in the right shoulder. This was accompanied by nausea and vomiting of undigested food. Since her entry she has had continued severe, unrelieved pain, nausea, and vomiting. She had a similar attack three weeks before, but it was milder in nature. In her past history she has had much epigastric distress, burning, and gas following meals. There was also some fat intolerance.

On examination, temperature was 37° C., pulse 84, respiration 22, blood pressure 110/70. She was a very obese woman in acute abdominal distress. There was generalized spasm of the abdomen and extreme epigastric tenderness in the right upper quadrant with spasm. Referred and rebound pain to the right upper quadrant and periumbilical region. There was a positive Murphy's sign, no costovertebral angle pain or tenderness. White blood count was 13,800, icterus index 16 units, and amylase 4,000. Flat plate of the abdomen was negative.

She was confined to bed and treated with fluids parenterally with subsequent fall in the blood amylase level to 94. Her icterus index fell to 9 units. She was discharged May 26 to stay on a surgical soft and low-fat diet, with a diagnosis of acute pancreatitis and questionable acute cholecystitis. June 16, 1941, she was given an intravenous cholecystogram which showed a nonfunctioning gall bladder. A diagnosis of chronic cholecystitis was made. It was decided to operate upon her in the fall at her request. She remained symptom-free on a diet until three days before her second admission, which was Dec. 26, 1941. The appointment for operation in the fall was not kept, but on the date of this admission she had an acute mid-upper abdominal pain with radiation to the back, associated with nausea but no vomiting. The attack lasted for about two hours. She had a similar attack on the day prior to admission and on the evening of admission had the third attack. She thought these attacks were brought on by taking some cream with her food. Cholecystectomy and exploration of the common duct were carried out. An acute and chronic gall bladder, and cholecystitis with cholelithiasis were demonstrated. The gall bladder was packed full of hundreds of small faceted stones. Following operation she has done very well and has remained symptom-free to date.

M. R. (Hospital No. 205096), a 52-year-old obese, Irish woman, was admitted May 20, 1943. She gave a five-year history of head pain and indigestion with two acute attacks accompanied by nausea, vomiting, and acholic stools. Following a fatty meal she had onset of intermittent epigastric pain localized in the right upper

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Post-mortem examination showed a peripancreatic abscess, a retroperitoneal abscess, a perforation of the colon next to the abscess, and a small stone in the common bile duct, with the wall of the abscess containing many bowel loops, chronic pancreatitis, and fat necrosis over the peritoneum.

J. S. (Hospital No. 176444), a 69-year-old obese woman, was admitted to the hospital April 9, 1941. She had severe pain in her back and abdomen over a period of the last five years, coming on approximately once a month and lasting four to five days, then disappearing spontaneously. Five days previous to admission she had severe pain in the lower abdomen which she had never had previously. This persisted until her admission, keeping her awake at night. She said the pain was greater in the right lower quadrant but was indefinite as to its situation. Associated with this there was also marked back pain which had been constant. The patient had been confined to bed. There had been no nausea, vomiting, constipation, injury, genitourinary symptoms, or gall bladder history. Her appetite had been poor and she had taken mostly liquids, with the result that she has lost about twenty pounds in the last year.

On entry her temperature was 37° C., pulse 100, respiration 22, and blood pressure 115/70. She appeared to be in considerable pain. Her skin was dry and flushed. She showed generalized arteriosclerosis and arteriosclerotic heart disease, class 2-A. Her abdomen was rounded, diffusely tender with spasm and marked tenderness at the dorsal-lumbar spine, both sides. No masses or viscera were palpable. There was a question of fluid in the abdominal cavity and marked distention. A tender mass was thought to be felt in the right upper quadrant. She showed mild diabetes. While blood count was 17,000. Amylase test was done and showed 130. Icterus index was 8, nonprotein nitrogen, 133, and a flat plate of the abdomen was negative. There was little from which to make a diagnosis, according to the consultant who attended, but it was suspected that the patient had an acute pancreatitis in spite of the low amylase test.

Two x-ray treatments of 100 r. each were given over the pancreas. Under local anesthesia a large amount of prune juice fluid was obtained. A normal gall bladder was noted. There were fat necroses in the omentum, one piece of which was biopsied and showed fat necrosis microscopically.

She was treated with parenteral fluids and insulin with a good response. Her postoperative course was marked by daily elevation of temperature and one episode of decompensation of her heart which required digitalis for control. She continued to be lethargic for a couple of days postoperatively. Her course was fairly good although a large tender mass was present in her abdomen which was considered to represent pancreatic abscess. On the twenty-sixth day she had acute abdominal pain and the passage of clotted blood per rectum and coffee-ground vomiting. The patient went rapidly into shock and did not respond to therapy. She died on the twenty-sixth postoperative day, or exactly one month after admission.

At post-mortem she showed acute hemorrhagic pancreatitis with extensive fat necrosis, perforation of the duodenum, and transverse colon. There was a perinephric abscess on the right side and chronic cholecystitis and cholelithiasis with impacted stones in her cystic duct.

A. F. (Hospital No. 180482) was a 65-year-old, well-nourished man. While walking, he had a sudden, severe pain in the pit of his stomach. It spread through his entire abdomen. He got relief by lying on his left side and remaining quiet. This pain was of twelve hours' duration when he was admitted to the emergency department. He was vomiting a coffee-ground material continuously if he took anything by mouth. He was pale, in acute distress, perspiring, and anxious. There were slow, thready pulse, diffuse tenderness of the abdomen, spasm, and rebound tenderness. There was no distension although liver dullness could not be definitely made out. A flat plate of the abdomen showed no free air and no trapped air in terminal

loops. Temperature was 38° C., pulse 80, respiration 24, blood pressure 120/80, icterus index 20, and amylase 2,600. His referring diagnosis was ruptured peptic ulcer.

He was given four treatments of 100 r. each by x-ray and his amylase dropped from 2,600 to 1,280. He made a steady improvement. His pain disappeared after the third day. He was well hydrated, comfortable, and on a house diet. On the fifteenth hospital day he had an attack. His temperature went to 40.5° C. Amylase at this time was 1,778, icteric index 36. He had crampy pain. This was undoubtedly an attack of recurrent pancreatitis. He was treated again as previously. He became afebrile, his icterus subsided, and one week later an intravenous cholecystogram was done, following which he had a steady downhill course and died on the thirtieth hospital day. Post-mortem examination was not obtained.

C. V. (Hospital No. 35226), a 48-year-old well-nourished woman who was a pernicious anemia patient, was admitted to the hospital. Fifteen hours before, she had upper abdominal pain which was the fourth and severest attack of this kind in the last year. There were persistent vomiting of bilious material and pain which ran from the left to the right. Thirty years before she had jaundice. Her vital signs were normal. She had epigastric tenderness and moderate spasm, more prominent on the right than on the left side. There was a positive Murphy's sign. Blood pressure was 160/88, white blood count 13,000, amylase 1,200, icterus index 16. Without waiting for the result of the amylase test, operation was carried out. Serosanguineous fluid was present in large amounts. Gall bladder was thin. There were no stones. Pancreas was enlarged, edematous, and had a yellow-greenish discoloration. Amylase on the abdominal fluid was 2,700. Following operation the patient was given x-ray over the pancreas and the amylase test dropped to normal within three days; she was discharged on the fourteenth day in good condition.

In August, 1941, she had an attack which was similar to this and went to a hospital in Auburn where a former resident of this hospital worked. He made a diagnosis of an acute pancreatitis. The attack subsided in four days and she was discharged from the hospital. She has been followed in the pernicious anemia clinic since that time and was well to October, 1944.

J. S. (Hospital No. 120402), a 62-year-old rather obese woman, Oct. 12, 1936, had a definite attack of acute pancreatitis diagnosed by operation. Fat necrosis was present at that time, as well as edema of the pancreas. Since then she has had gas after eating regularly. Three hours before admission, she had an acute abdominal pain localized in the upper abdomen, severe, generalized associated with nausea but no vomiting. She was in acute distress, appeared to be in shock. She had cold, clammy extremities. There was slight distention. Tenderness was general and there was spasm in the right upper quadrant. The liver dullness was not obliterated. Temperature was 36.6° C., pulse 84, respiration 24, blood pressure 115/68, icterus index 18, white blood count 25,000, and amylase 4,000.

She was given 300 r. x-ray treatment over the pancreas and the following day her amylase had dropped to 1,200 and by the third day was in the range of normal. Her tenderness subsided but distention remained. She was allowed up and gradually became normal. A gall bladder series was taken December 10 and showed stones in the gall bladder. Cholecystectomy with exploration of the common duct was done. There were visible fat necroses present and the pancreas was seen to be firm, rough, and nodular. She responded well to operation and was discharged home well. She has been well to date. This woman has had two attacks of acute pancreatitis.

F. B. (Hospital No. 173081), a 40-year-old obese woman, was admitted to the hospital complaining of sharp pain in the shoulders and back and between the shoulder blades, of five weeks' duration. She had pains in the chest for the last five weeks, also with persistent cough. She had para-umbilical pain for five weeks

and two days before admission it became very sharp, something having "let go" in her left abdomen. She had severe sharp pain after that, vomiting, hot burning pain, and diarrhea. In her past history she had a bad heart, rheumatic heart disease. Temperature was 38.6° C., pulse 96, respiration 20, white count 10,000. She was in acute pain. There was generalized abdominal tenderness which was increased to the left of the umbilicus and in the left upper quadrant there was a firm, herniated mass at the umbilicus, tender to touch. She kept her left leg flexed for relief. A diagnosis of incarcerated omentum and strangulated hernia was made.

Under vinethene and local anesthesia the hernial sac was opened. A strangulated omentum, greatly thickened and hemorrhagic, was dissected away from the colon. For six days she was afebrile and comfortable. Then she developed fever and moderate pain again. There was moderate distention, tenderness and pain in the right upper quadrant, moderate umbilical pain and muscle spasm, and free fluid which was sterile to culture. The question of pancreatitis was raised. For one month she had fever and pain which was severe and constant, finally slowly improving. About three-fourths of the way along her course an amylase test was taken which showed a reading of 540 and repeated tests showed it never below 420. Microscopic examination showed acute and chronic organizing inflammation of the omentum and sterile fluid. She was discharged one month after entry in good condition. This was undoubtedly the result of an acute pancreatitis with resolution of widespread inflammatory reaction.

M. T. (Hospital No. 125461), a 48-year-old slightly obese woman, was admitted to the emergency department April 10, 1941. She had sudden, severe, epigastric pain starting four hours previously, radiating to her back and to the left. She had two spells of vomiting. The pain went to the left costovertebral angle also. Her symptoms suggested "intestinal obstruction." Temperature was 37° C., pulse 86, respiration 24, blood pressure 150/95. She was uncooperative and complaining, rolling about in bed and moaning. Her abdomen was large and rounded. There was no free fluid present. She had tenderness at the left costovertebral angle and diffuse abdominal tenderness. There was no spasm or mass at entry. Her icterus index was 7, white blood count 16,000. The diagnoses suggested were: gall bladder infection, posterior perforated ulcer, partial intestinal obstruction, kidney stones, pancreatitis, ovarian cyst. She was admitted to the hospital and her amylase test showed 3,200. A course of x-ray therapy was given to her, consisting of 100 r. units, six times. Coincident with this treatment there was a rapid drop in her amylase from the initial figure to 80. She refused operation. After the condition had subsided, she was in the hospital for about one month, and during that time a mass was palpable in her right upper quadrant. This was thought to be either a distended gall bladder or perhaps an abscess in the region of the pancreas. However, she continued to refuse operation and was discharged in the latter part of May, 1941. At the last report the patient still refused to accept advice but was having considerable indigestion and symptoms of chronic cholecystitis in attacks. She was last seen in April, 1942, at which time she remained about the same as she had been previously.

CONCLUSIONS

Pancreatitis must be considered as a possibility in patients complaining of sudden severe epigastric pain.

The serum amylase test is of the greatest assistance in deciding whether the pancreas is involved.

The test is easily carried out, is accurate, and gives more important information than any of the routine laboratory tests.

Clinically, there are two distinct pathologic types of acute pancreatitis, acute edematous and pancreatic necrosis.

Acute edematous pancreatitis can be diagnosed by the serum amylase test and the rapid improvement under conservative treatment.

Pancreatic necrosis must be suspected when the patient fails to make improvement within a few days.

In acute edematous pancreatitis operation should be deferred until the reaction has subsided.

Acute edematous pancreatitis is followed by chronic pancreatitis frequently, as is demonstrated at late operation.

Pancreatic necrosis is followed by abscess, diabetes, and pseudocysts in a proportion of those who survive.

Conservative treatment of pancreatic necrosis or pancreatic abscess is disastrous.

When diagnosis of either condition is suspected, operation is indicated as soon as the patient can be properly prepared for it.

Biliary tract disease should be treated after an acute pancreatitis attack if it has played a part in the onset.

Any surgical manipulation about the lower end of the common duct or the head of the pancreas is likely to be followed by postoperative acute pancreatic edema.

This can be demonstrated by the amylase test.

There is a considerable danger of this in the resection of posterior duodenal ulcer perforating into the pancreas.

It carries a mortality which should be taken into consideration in any series of duodenal ulcer resections.

The case reports were selected to illustrate points made in this discussion.

REFERENCES

1. Ackerman, L. V.: Acute Pancreatitis Following Blood Transfusion, *Arch. Path.* 34: 1065-1069, 1942.
2. Bisgard, J. D., and Baker, C. D.: Studies Relating to the Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis, *Ann. Surg.* 112: 1006-1034, 1940.
3. Brodie, N. N., and Ficarra, B. J.: Acute Hemorrhagic Pancreatitis, a new Etiological Concept and Case Report, *Am. J. Surg.* 63: 394-397, 1944.
4. Brütt, H.: Konservativ oder operative Behandlung der akuten pankreasnekrose? *Zentralbl. f. Chir.* 66: 1122-1126, 1939.
5. Carter, R. T., and Hotz, R.: Pancreatitis and Biliary Tract Disease, *Am. J. Surg.* 44: 719-722, 1939.
6. Casberg, M. A.: Acute Pancreatic Necrosis and Acute Interstitial Pancreatitis; Treatment Without Operation, *Arch. Surg.* 39: 247-263, 1939.
7. Clark, E.: Pancreatitis in Acute and Chronic Alcoholism, *Am. J. Digest. Dis.* 9: 428-431, 1942.
8. Connell, F. G.: Acute Pancreatitis With Fat Necrosis, *Am. J. Digest. Dis.* 8: 327-328, 1941.
9. Dinsmore, R. S., and Nosik, W. A.: Pain in Acute Pancreatitis, *S. Clin. North America* 19: 1253-1261, 1939.
10. (a) Elman, R.: Nitroglycerin in Treatment of Acute Pancreatitis, *Am. J. Digest. Dis.* 6: 474-475, 1939.
(b) Idem, Surgical Aspects of Acute Pancreatitis, *J. A. M. A.* 118: 1265-1268, 1942.

11. (a) Fallis, L. S.: Acute Pancreatitis, *Am. J. Surg.* 46: 593-599, 1939.
(b) Fallis, L. S., and Plain, G.: Acute Pancreatitis, *SURGERY* 5: 358-373, 1939.
12. Gaither, E. H.: Etiology, Diagnosis and Medical Management of Pancreatic Disease, *Am. J. Digest. Dis.* 6: 429-434, 1939.
13. Gaskell, J. F.: Acute Hemorrhagic Pancreatitis as a Cause of Sudden Death, *Clin. J.* 71: 12-18, 1942.
14. Gottesman, J., Casten, D., and Beller, A. J.: Changes in Electrocardiogram Induced by Acute Pancreatitis, *J. A. M. A.* 123: 892-894, 1943.
15. Griessmann, H.: Zur diagnose und therapie der akuter pankreasekrankungen, *Deutsche Ztschr. f. Chir.* 252: 19-40, 1939.
16. Ireneus, C.: Experimental Bile Pancreatitis With Special Reference to Recovery and to Toxicity of Hemorrhagic Exudate, *Arch. Surg.* 42: 126-140, 1941.
17. Johnson, T. A., and Bockus, H. L.: Serum Lipase Test, *Am. J. Digest. Dis.* 10: 1-7, 1943.
18. Jones, R. Jr.: Etiology and Pathogenesis of Acute Hemorrhagic Pancreatitis. *Am. J. M. Sc.* 205: 277-301, 1943.
19. Lampson, R. S.: Acute Pancreatitis, *Ann. Surg.* 116: 367-372, 1942.
20. Lynch, K. M.: Pancreatitis, an analysis of Types and Causes, *Ann. Int. Med.* 14: 628-640, 1940.
21. (a) McCorkle, H., Goldman, L., and Cornell, R. N.: Significance of Determinations of Serum Amylase in Acute Pancreatitis, *Clinics* 1: 756-761, 1942.
(b) McCorkle, H., and Goldman, L.: Clinical Significance of Serum Amylase Test in Diagnosis of Acute Pancreatitis, *Surg., Gynec. & Obst.* 74: 439-455, 1942.
22. Morley, J., Yates, H. B., and Ogilvie, W. H.: Acute Pancreatitis. *Proc. Roy. Soc. Med.* 32: 670-681, 1939.
23. (a) Morton, J. J.: Acute Pancreatitis, *New York State J. Med.* 40: 255-263, 1940.
(b) Morton, J. J., and Widger, S.: The Diagnosis and Treatment of Acute Pancreatitis, *Ann. Surg.* 111: 851-863, 1940.
24. Ogilvie, R. F.: Duodenal Diverticula and Their Complications With Particular Reference to Acute Pancreatic Necrosis, *Brit. J. Surg.* 28: 362-369, 1941.
25. Polowe, D.: Blood Amylase, *Am. J. Clin. Path.* 13: 288-301, 1943.
26. (a) Popper, H. L.: Etiology of Acute Pancreatitis, *Am. J. Digest. Dis.* 9: 186-187, 1942.
(b) Popper, H. L., and Plotke, F.: Observation on the Disappearance of Experimentally Increased Blood Amylase and Lipase, *SURGERY* 9: 706-711, 1941.
27. Probstein, J. G., Wheeler, P. A., and Gray, S. H.: Perforated Peptic Ulcer; Its Differentiation From Acute Pancreatitis by Blood Diastase Determination, *J. Lab. & Clin. Med.* 24: 449-452, 1939.
28. Reichl, E.: Zur Klinik und Therapie der akuten Pankreasnekrose, *Arch. f. klin. chir.* 197: 428-447, 1939.
29. Shumacker, H. B.: Acute Pancreatitis and Diabetes, *Ann. Surg.* 112: 177-200, 1940.
30. Smyth, C. J.: Etiology of Acute Hemorrhagic Pancreatitis With Special Reference to the Vascular Factors, *Arch. Path.* 30: 651-669, 1940.
31. (a) Somogyi, M.: Micromethods for Estimation of Diastase, *J. Biol. Chem.* 125: 399-414, 1938.
(b) Idem: Diastatic Activity of Human Blood, *Arch. Int. Med.* 67: 665-679, 1941.
32. Whipple, G. H., and Goodpasture, E. W.: Acute Hemorrhagic Pancreatitis, *Surg., Gynec. & Obst.* 17: 541-547, 1913.

INVESTIGATION OF THE CAUSE AND PREVENTION OF GAS PAINS FOLLOWING ABDOMINAL OPERATION

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IN THE immediate convalescence from the routine type of abdominal operation the most common causes of distress are gas pains, nausea, and vomiting; they are of such usual occurrence that they are accepted as a matter of course and little is done to alleviate them. Both distressing conditions can be prevented to a great degree by proper procedure. For a time after abdominal operations there is decreased motility of the bowel; therefore, any gas in the bowel remains there, causing distention and pain.

In a group of patients at the University Hospital a few years ago, observations on the motility of the bowel after appendectomy were conducted by one of us (H. H. D.). In a series of cases in which appendectomies were performed under spinal anesthesia, each patient was given a small quantity of barium a few days before operation and its passage through the intestinal tract watched. The same quantity of barium was given immediately after operation and its progress observed. At the end of two hours the stomach was empty in 64 per cent of the patients in the control group, and it was empty in only 20 per cent of the patients in the operative group. At the end of twenty-six hours, we found that usually the barium had entered the rectum in the patients in the control group; it was in the ascending and transverse colon in those of the operative group. At the end of two days the stomach was empty in the patients in the control group, but the barium was in the transverse colon and the sigmoid in those of the operative group. It was evident that a definite decrease in peristalsis followed even a simple appendectomy.

Puestow,¹ in his work on peristalsis, showed a contrary motility between the small and large bowel, that is, the small and large bowels were not stimulated by the same drugs. He found the small bowel was stimulated, but the colon was inhibited by opiates, physostigmine, prostigmine, methylsulfate, and choline derivatives. Pitressin stimulated the colon but inhibited the small bowel.

In the past there has been an erroneous belief that the intestinal gases were the result of putrefaction arising in the bowel. In 1918, as a result of his experiments with animals, Kantor² showed that swallowed air is the main source of gas in the bowel.

In 1926, McIver, Benedict, and Cline³ analyzed gases withdrawn from the rectum in postoperative patients with distention and in nonsurgical

patients. They found that the percentage of nitrogen was uniformly high. Since free nitrogen is liberated in the intestines in small quantities, if at all, it must be derived from air, 79 per cent of which is nitrogen.

In 1934 Hibbard and Wangenstein¹ analyzed the composition of gas in the patient with distention and found that it was: carbon dioxide 6 to 12 per cent, oxygen 10 to 12 per cent, methane and hydrogen low, and nitrogen 70 per cent. Hibbard and Wangenstein concluded that 68 per cent of the gas in the bowel was due to swallowed air. In 1942, Singleton, Rogers, and Houston⁵ conducted a similar experiment and found: carbon dioxide 9.51 per cent, oxygen 5 per cent, methane 1.2 per cent, and nitrogen 84 per cent. The source of the nitrogen was considered to be swallowed air.

Wangensteen and Rea,⁶ in 1939, noted that with cervical esophagostomy there was no excess gas in the obstructed intestines. It has been noted, also, that in patients with complete esophageal strictures abdominal operations resulted in no gas in the bowel, and there was no tendency toward distention.

Much of the air which is swallowed is done so in the induction phase of anesthesia. Were the patient not under the influence of sedatives prior to induction, the amount of air swallowed would be much higher. Uneasiness, excitement or resistance on the part of the patient is conducive to the swallowing of air.

Proceeding upon the hypothesis that the swallowed air is the cause of gas in the bowel, we carried out a series of clinical experiments at the Immanuel Hospital.

The Levin tube was inserted one-half hour after the patient had received a preoperative hypodermic of pantopon, gr. $\frac{1}{3}$, and scopolamine, gr. 1/100. Thus the patient was semiconscious and relaxed and did not resist. Patients have been taken to the operating room and returned, not knowing that the tube had been inserted and was functioning. In the operating room the Levin tube was connected with the bottles for gastric suction. By measuring the amount of water displaced in the bottle by the Wangenstein technique, the amount of air swallowed by the patient was determined.

One of the problems encountered concerned the length of time the tube should be retained by the patient. The average of sixty-four hours (See Table I), we found to be too long. This average resulted because of experimental attempts to find the ideal time for removal, the span being from twenty-four to seventy hours, or longer. Careful attention to the Wangenstein fluid balance helped to determine the ideal time for removal. At first, more fluid came back by Wangenstein suction than the patient swallowed, but during the first, second, or third day, depending on the patient, we found that the patient was drinking more than the suction could remove. This indicated that the material was going past the pyloric sphincter. The character of the stomach contents changed

TABLE I

	NUMBER OF PATIENTS	C.C. AIR DURING INDUCTION	AV. AIR DURING INDUCTION	C.C. AIR DURING OPERATION	AV. AIR DURING OPERATION	TOTAL AIR SWALLOWED	AV. AIR SWALLOWED	NUMBER HOURS LEVIN TUBE	AV. NUMBER HOURS LEVIN TUBE
Pelvic operations	14	3200	228.57	2500	178.57	5700	407.14	774	55.29
Cholecystectomies	14	800	57.14	1900	135.71	2700	192.86	824	58.88
Resection and Colostomy	5	250	50.00	1150	230.00	1400	280.00	444	74.00
Miscellaneous	12	1650	137.50	1775	148.08	3425	285.42	815	68.00
Appendectomies	8	850	106.25	265	44.25	1115	150.50	874	62.44
Totals	53		126.42	143	143.23		269.65		64.09

The miscellaneous here are all Intraperitoneal surgery.

at this time. During the first hours following surgery there was a considerable amount of bile returned, but at the time more fluids were taken than returned by Wangenstein suction, the stomach contents returned clear, no longer bile stained, which indicated that there was no regurgitation from the duodenum. The time to remove the tube was indicated when a positive fluid balance, with no bile in the stomach contents, was achieved.

In the series included in this experiment, one patient who had an appendectomy swallowed 700 c.c. of air during induction; there were no postoperative complaints. A cholecystectomy patient who swallowed 600 c.c. of air complained of some gas pains which were relieved with atropine. In a subsequent operation, a stenosis of the sphincter of Oddi was found which may have been a contributing factor to the postoperative distress. During anesthesia for hysterectomy, a woman swallowed 1,000 c.c. of air; she complained of gas pains on the second day following removal of the tube, which had been removed at forty-eight hours. She was given four doses of pitressin for relief of gas pains. Another patient in whom we loosened some adhesions for partial obstruction, swallowed 2,150 c.c. of air; there were no complaints following surgery. A woman with bilateral oophorectomy swallowed 1,900 c.c. of air, and she had no complaints. Another with a cholecystectomy swallowed 600 c.c. of air; she vomited nine ounces on the first postoperative day, but was drinking water faster than the Wangenstein suction could remove it. She drank a total of 8,000 c.c. of water on the first postoperative day. These patients were fairly comfortable and had no distention because the air was removed immediately rather than allowed to go down into the bowel. Once the air has passed into the bowel it is too late to get complete relief by Wangenstein suction.

Apparently the only disadvantage in the use of the Wangenstein suction is the slight discomfort experienced by the patient because of throat irritation due to the tube. However, in one patient, the tube was removed because of this irritation and within twelve hours the

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The following is a list of the names of the persons who have been appointed to the various positions in the various departments of the Government of the State of New York, for the year 1900.

With the Wangensteen suction 5 patients, or 10 per cent, were distended with gas. Of these, 4 had been operated upon for intestinal obstruction, either complete or partial, and had moderate distention prior to surgery. In the group without Wangensteen suction there was distention in 29 per cent.

It has been mentioned previously that as a bowel stimulant for the reduction of gas, prostigmine is specific for the small bowel and pitressin for the large bowel. Prior to the use of the Wangensteen suction these drugs were used extensively for the attempted reduction of gas and distention. Sixty-four doses of pitressin, one-half ampule per dose, were used in fifteen patients in a control group. Twenty-four ampules of prostigmine were used in 4 patients. Of these, 11 had no distention prior to surgery. The categories of those who had received the drug were: cholecystectomy, 6 patients; pelvic operation, 5 patients; exploratory celiotomy, 4 patients. After the use of the Wangensteen suction was adopted, only 2 patients were given pitressin. Of the twenty-seven doses administered, 1 patient with distention before surgery received twenty-five.

Analyzing our control series, we found that the Wangensteen suction was used in 25 patients. Eight of these patients had either bowel resection or gastrectomy. In the other 17 it was used in an attempt to reduce distention after it had once begun. We now believe this to be ineffective. It has been the practice of many surgeons to pass the Wangensteen tube if the patient had marked distention and had severe gas pains, but in those in whom the gas had passed from the stomach into the bowel only partial relief was achieved because the Wangensteen tube did not reach into the bowel. With the Wangensteen suction functioning prior to anesthesia, gas is drawn out of the stomach before it has passed into the bowel and distention is prevented. This is particularly true in cases of obstruction of the bowel. Therefore, the Wangensteen suction should be used for the prevention of gas and the Miller-Abbott tube for the reduction of distention once it has developed.

A marked reduction in the need for rectal tubes, flushes, and enemas was observed. Collier, in a discussion on the subject, made the following remark: "As far as I know, enemas do nothing but exhaust the patient and stimulate reverse peristalsis and increase distention, and the rectal tube does nothing but cause piles."⁵

It is impossible to tabulate the clinical response of the patient. However, it was noted that, comparatively, these patients made better progress, felt better, and required less attention.

Wangensteen suction usually is unnecessary in appendectomies and herniorrhaphies since there is generally a minimum amount of gas and distention. The routine use of Wangensteen suction in appendectomies has been discontinued, but if there are signs of peritonitis it is passed immediately.

CONCLUSIONS

Immediately following abdominal operations there is some paresis of the bowel wall so that gas is not passed along the bowel properly, to be expelled. Therefore, it collects, causing distention, pain, and, at times, vomiting.

Swallowed air is the main source of gas in the bowel following operations. It is advised to institute Wangensteen suction during the anesthesia and surgical procedure, as well as in the immediate postoperative period, to evacuate the gas as it enters the stomach, and so prevent its entrance into the bowel.

REFERENCES

1. Puestow, Charles Bernard: Intestinal Motility and Post-Operative Distention; Experimental and Clinical Studies, *J. A. M. A.* 120: 903-908, 1942.
2. Kantor, John L. A.: Study of Atmospheric Air in Upper Digestive Tract, *Am. J. M. Sc.* 155: 829-855, 1918.
3. McIver, M. A., Benedict, E. B., and Cline, J. W.: Postoperative Gaseous Distention of Intestine, *Arch. Surg.* 13: 589-604, 1926.
4. Hibbard, J. S., and Wangensteen, O. H.: Character of Gaseous Distention in Mechanical Obstruction of the Small Intestine, *Proc. Soc. Exper. Biol. & Med.* 31: 1063-1066, 1934.
5. Singleton, Albert O., Rogers, Funsten, and Houston, Forrest Gish: The Problem of Intestinal Gases Complicating Abdominal Surgery, *Ann. Surg.* 115: 921-934, 1942.
6. Wangensteen, O. H., and Rea, C. E.: The Distention Factor in Single Intestinal Obstruction, *SURGERY* 5: 327-339, 1939.

GASTRIC RESECTION FOR CERTAIN ACUTE PERFORATED LESIONS OF STOMACH AND DUODENUM WITH DIFFUSE SOILING OF THE PERITONEAL CAVITY

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FOR many years there appeared to be a geosurgical problem in the surgical management of peptic ulcers. The ulcers in peoples of continental Europe seemed to differ in certain respects, particularly in response to therapy, from those of the peoples of English-speaking nations. American and British surgeons were convinced that they obtained satisfactory results from the conservative operations of simple excision, gastroenterostomy, and pyloroplasty; whereas the surgeons of continental Europe learned very early that these procedures gave unsatisfactory results in their patients, and for the most part, they abandoned them in favor of the more radical operations of resection. To account for this apparent difference, several explanations were offered, among them differences of temperament, custom, diet, and associated gastritis.

However, in recent years as the surgeons of this country have accumulated an experience with gastric resection for peptic ulcers, and have had an opportunity to compare the late results of this operation with those obtained by the conservative procedures, they have become convinced, as were the surgeons of continental Europe, that resection produces a much higher percentage of permanent cures with no significant increase in operative mortality.

For more than a decade many German and Russian surgeons have followed the same radical course in the treatment of acute perforated ulcers. They have done emergency resections in the presence of diffuse soiling in all but the poorer risk cases and with a mortality which seems almost incredibly low. As a matter of fact, the reported mortality from resection has been definitely lower than that from simple closure of the perforations. DeBakey, in 1940, in an exhaustive review of the literature, collected 2,392 cases in which resection was done with a mortality rate of 13.4 per cent, and 5,589 cases of simple closure of perforation with a mortality rate of 25.9 per cent. It must be borne in mind that those in which resection was done represented a selected group in which the poorer risks were excluded. Judine, in 1937, however, reported a series of 418 cases of which 331 were good-risk patients, treated by resections with a mortality of 7.8 per cent, and 87 were poor risks, treated by simple closure or simple closure plus gastroenterostomy with a mortality of 32.2, giving an over-all mortality of only 12.8 per cent. Two years later he reported his own remarkable experience with 937 cases of resection, with a mortality of 8.9 per cent. Even lower mortality rates have been reported. Mulleder and Neuberger reported 21 cases of resection with 4.8 per cent mortality, and Odelberg, 20 cases of

resection with 5 per cent mortality. Mortality rates under 14 per cent have been reported by von Haberer, Paul, Hromada and Newman, Gerhardt, Kochl, Marine, Peters, Rieder, Sostegni, Steiger, and several others. There are a few unusually low mortality figures reported for small series of cases in which the patients were treated by simple closure; Tilton, 2 per cent; Graham, 2 per cent; Pich, 2 per cent; Nicholas, 3.6 per cent; Gilmour, and Saint, 4.7 per cent; and Black, 5.4 per cent.

The advocates of primary emergency resection contend that not only is the immediate mortality less and certainly no greater than that of primary closure, but that the operation is curative rather than palliative. There is a high incidence of recurrent ulcer symptoms following simple closure, contrary to general opinion. In DeBakey's large collected series of followed cases, gastrectomy resulted in long-term relief of symptoms in 90.6 per cent of patients so treated; simple closure gave relief in only 65 per cent, and in 16.9 per cent of the simple closures subsequent operations were necessary. Harrison and Cooper have reported recurrence of symptoms in 82.5 per cent of cases following simple closure and Parker found that subsequent operations were necessary in 34 per cent of the simple closures he analyzed. The follow-up studies of cases in which resection was done, reported by Paul, Marine, and Odelberg, have indicated permanent cure in 100, 100, and 87 per cent, respectively.

These comparative figures are significant not as a basis for choosing between the two procedures, but rather as evidence that resection may be accomplished in the presence of a chemical peritonitis with little or no increase of hazard in the hands of skilled resectionists. It is not a matter of making a choice between the two procedures and establishing this choice as a routine. I believe that both procedures have definite roles in the management of these emergencies. I believe that the immediate interest of most cases is best served by simple closure of the perforation and that the high incidence of recurrence is not a deterrent. Recurrent ulcers requiring a subsequent resection can be handled by elective operations with less risk.

There are a few cases, however, in which primary resection is either the operation of choice or is definitely imperative. It is the purpose of this paper to present these indications with illustrative cases. These indications are:

1. Perforated carcinoma of the stomach
 - (a) Delimited-resectable lesions
2. Perforated peptic ulcers associated with recent or simultaneous gross hemorrhage
3. Perforated peptic ulcers associated with fixed pyloric obstruction
4. Recurring perforations
5. Perforations with insignificant soiling
6. Very early perforation in the very young

Probably under no circumstances should resection be undertaken unless the patient is in fair condition, preferably young, and the perforation of not over twelve hours' duration.

PERFORATED CARCINOMAS

Acute perforation of a carcinoma of the stomach into the free peritoneal cavity occurs very infrequently. I have had the unusual experience of encountering two cases at operation. The first one was reported in 1944.²

One hundred twenty years ago Laennec recorded in his case book an instance of perforation of carcinoma of the stomach with peritonitis. Since then the case reports which have appeared in the literature have been collected periodically. In 1935, Aird reviewed previous analyses and assembled seventy-one reported cases. To these he added one of his own and seven others from the Royal Infirmary at Edinburgh.

From a review of the literature since 1934, in collaboration with Overmiller, I have collected an additional 138 cases in which the diagnosis had been established at operation or post-mortem examination. In approximately one-half of these cases no operation had been performed.

The combined series of 217 cases gives an erroneous conception of the incidence of perforation. Unquestionably only a few of the total number of cases have been reported. A more accurate impression can be gained from several available surveys of case records and autopsy reports. In these the incidence varies from 2.8 to 6 per cent, as follows: Brinton, 21 perforations in a total series of 507 cases of carcinoma of the stomach; Ditrich, 7 in 110; Lang, 12 in 210; Toinon, 9 in 255; Jaisson, 6 in 135; McNealy and Hedin, 116 in 3,289, and Casberg, 7 in 247.

In only 7 of the 217 cases was it alleged that a correct diagnosis had been made prior to operation or post-mortem examination. More astonishing was the failure, in many instances, to recognize at operation that perforation had occurred in a carcinomatous crater instead of a benign peptic ulcer. The failure to recognize the presence of the carcinoma suggests that many of the carcinomas which perforate are small and relatively confined lesions presumably suitable for resection. This premise has been borne out at the autopsy table. In these cases there is, therefore, the possibility of considerable salvage of life.

From the study of 46 case histories collected from the literature, Chavannaz and Radoiévitsh distinguished four clinical types: (1) cases with a sudden onset of severe epigastric pain and manifesting the typical signs of a perforated peptic ulcer, this preceded by a long or short history of dyspepsia; (2) cases differing from (1) only in respect to absence of previous dyspepsia; (3) cases with an insidious onset exhibiting signs of a gradually progressive peritonitis; (4) cases in which the

patients die of peritonitis and at no time have symptoms to direct attention to the abdomen. About 70 per cent of the cases are types (1) and (2).

Records of gastric analyses were presented in eight of the histories reviewed by Aird and in fifteen of our collection. It is interesting that achlorhydria was present in only four cases, and that in most of the cases the acids were normal or excessive. This finding has been offered as further evidence that carcinomas which arise in the presence of normal acids are ulcer-carcinomas and arise in pre-existent peptic ulcers. It can also be reasoned that a penetrating peptic ulcer can develop in a carcinoma. The break in the mucosa initiated by a new growth exposes the underlying tissue to the digestive action of the gastric secretions which may rapidly penetrate the wall and be responsible for the perforation. Irrespective of this academic question certain facts stand out. The patients with normal and high acids had long histories of dyspepsia, usually typical of ulcer, and upon perforation presented a clinical picture and pursued a course identical with that of perforated peptic ulcer.

Too little data are available to determine definitely the influence of achlorhydria. Such as there is, suggests that carcinoma in the absence of acid perforate as a result of necrosis rather than ulceration and the perforation is likely to be relatively painless and silent, or if sudden and painful, then rapidly fatal from septic peritonitis.

The two important problems relating to perforated carcinomas of the stomach are first, recognition of the carcinoma by routine biopsy and second, operative management. In approximately 50 per cent of cases a hopelessly incurable situation exists because of advanced peritonitis from septic soiling or delayed intervention or because the tumor is not resectable.

There is no question about the desirability of resection of resectable lesions—only a question of when it should be done. In an endeavor to answer this question the results of the various methods of management used in 115 operations in cases of the collected series are shown in Table I.

TABLE I*

	RECOVERED	HOSPITAL DEATHS
Drainage alone	3	15
Simple closure (with or without drainage)	9	34
Local excision with simple closure	2	4
Simple closure and gastroenterostomy	7	16
Simple closure and jejunostomy	0	2
Jejunostomy alone	0	2
Primary simple closure and resection at subsequent operation		
Planned	1	1
Corrected*	2	2
Primary resection	13	2
Total	37	78

*Perforation at primary operation was misdiagnosed peptic ulcer and proved malignant by subsequent developments and studies.

A mortality of 80 per cent following simple closure of perforations is understandable. Several reports contained remarks about the difficulty in obtaining satisfactory closure. Because sutures cut through the rigid and friable carcinomatous tissue, a few surgeons had to resort to suturing a patch of omentum over the perforation. In most instances post-mortem examination showed failure of healing with continued or subsequent leakage. This very considerable and inescapable hazard vitiates the theoretical advantage of the staged method of management; that is, emergency closure of the perforation by suture followed some days or weeks later by gastrectomy. In our collected series, 6 of the patients who recovered following primary closure were subsequently subjected to gastrectomy. Only 3 of them, or 50 per cent, survived. In 2 cases the two-staged procedure had been planned at the initial operation; in 4 the perforation had been closed in each instance upon the assumption that it was a perforated ulcer. After subsequent events and studies had proved these patients to have perforated carcinomas, resection was done. Furthermore, it is apparent from the histories that several additional patients who failed to survive simple closure had resectable lesions which probably would have been resected at a second operation.

For comparison with this record of two-stage management there are available in the literature the records of 15 primary resections, with the seemingly incredible result of only 2 fatalities, a mortality of only 13 per cent.

In the series of cases collected by Aird there were 7 primary gastrectomies with no mortality. McNealy and Hedin reported 7 primary gastrectomies with 2 fatalities in a group of cases collected by them from the records of Cook County and Wesley Memorial Hospitals. Both authors expressed the opinion that the superior results from primary gastric resection should be accepted with certain reservations. They believe that it was reasonable to assume that patients subjected to gastrectomy were in the most favorable general condition and that there is probably a tendency to report solitary successes and for the failures to be absent from the literature. These intangible factors in the available data make a comparative estimate of the merits of the single- and two-stage operation impossible. However, it is my opinion that the hazard of a gastrectomy in the presence of a diffusely soiled peritoneal cavity has been grossly overestimated and the hazard of leakage from a sutured perforation in carcinomatous tissue much underestimated.

CASE 1.—J. S., a Negro waiter, 49 years of age, was admitted to the hospital department of the Union Pacific Railroad, Dec. 6, 1942, writhing with generalized abdominal pain. The onset had been sudden, four hours previously, with severe pain in the epigastrium which diffused rapidly throughout the abdomen and then to the top of both shoulders. He had vomited a small amount of clear fluid soon after the onset.

He related that for one year he had had burning and gaseous distress in the epigastrium, which came on two or three hours after meals and during the night, and that this distress was relieved by the ingestion of food or alkalis.

On his admission, three months previously, a diagnosis of duodenal ulcer had been made upon the basis of a persistent deformity of the duodenal cap, with a 10 per cent five-hour gastric retention, normal free and total acids, and the repeated presence of occult blood in the stools. After ten days' hospitalization on an ulcer regime he was totally, if only temporarily, relieved of symptoms.

The patient presented the classical signs of perforated ulcer, with the confirmatory roentgenographic evidence of free gas in the peritoneal cavity.

Operation was performed one hour after admission and five hours after onset of symptoms. When the peritoneal cavity was opened there was an escape of much gas and "dishwater" fluid. The latter seeped from a diffused distribution throughout the abdomen. The stomach, delivered into the wound, presented a small perforation on the superior aspect of the anterior wall approximately three inches proximal to the pylorus. Palpation revealed that the perforation was located in the center of a crater the size of a silver dollar which had a wide, hard elevated border confluent inferiorly with a similar border surrounding a smaller crater. Except for a few glands in question along the lesser curvature, there was no evidence of metastases. A small piece of tissue was excised from the edge of the perforation and examined in frozen section. The pathologist returned a report of adenocarcinoma.

Confronted with a situation regarding which I had no knowledge, I reasoned that healing of a perforation through carcinomatous tissue would be unlikely and since the lesion appeared to be a very favorable one for resection, an immediate subtotal gastrectomy, even in the presence of a soiled peritoneal cavity, seemed a justifiable and logical procedure. Consequently, resection of the Polya-Balfour type was done. Five grams of sulfanilamide crystals were distributed over the peritoneal surfaces, and the peritoneal cavity was closed without drainage. The wound in the abdominal wall was washed copiously with saline solution, dusted with sulfanilamide crystals, and drained.

The pathologist's report of the specimen was as follows: A large segment of stomach with attached mesentery. Eight centimeters from the pylorus there was a crater which measured $4\frac{1}{2}$ cm. in diameter, with a central perforation the size of the head of a match. Adjacent was a smaller crater measuring $1\frac{1}{2}$ cm. in diameter. Both were surrounded by induration which disrupted the normal mucosal pattern. On the serosal surface there were thickening and fibrinous changes over the area of perforation. No glands containing carcinoma were found in the attached tissue. Sections from the borders of the crater show well-formed glands with well-differentiated cells containing hyperchromatic nuclei. There was occasional mitosis, and invasion of the muscularis. Diagnosis: Perforated ulcerating adenocarcinoma of the stomach, Grade II, with no metastases to nodes of the attached mesentery.

The immediate convalescence was entirely uneventful. Ten days following dismissal from the hospital the patient developed a fever and a pleuritic type of pain at the base of the right chest. He was readmitted to the hospital and a small right subphrenic abscess drained.

He returned to work in four months and remained free of symptoms and apparently well, for one year and four months. He then developed an ascites with general carcinomatosis peritonea and died twenty months following operation.

In this case, there was the advantage of a record of complete gastrointestinal studies three months prior to perforation. The normal acidity of the gastric contents which soiled the peritoneal cavity was probably

an important factor in preventing a bacterial peritonitis. The typical ulcer history of one year's duration, in addition to normal acidity, raises the question whether the carcinoma was the sole and primary lesion or had its origin in a pre-existent benign ulcer.

PERFORATED PEPTIC ULCERS

Associated Recent or Simultaneous Hemorrhage.—An impression of the incidence of hemorrhage in association with perforation can be gained from the report of McNealy and Howser. In their series of 700 cases there were 21 patients who had gross hemorrhages with the onset of perforation. In DeBakey's series of 2,525 cases, there were 155, or 6.1 per cent, incidences of hemorrhage. Simultaneous hemorrhages occurred in 16, or 10.5 per cent, of the 152 gastric perforations reviewed by Winters and Egan. Harrison and Cooper reported 8 instances out of a series of 57 cases. Five of these patients died immediately following the operation of simple closure and one subsequently had a fatal hemorrhage. As judged from this and similar references, hemorrhage contributes enormously to mortality and it would appear that simple closure of the perforation is inadequate because too often it fails to control the hemorrhage. Post-mortem examination has shown that these patients often have multiple ulcers and that hemorrhage usually arises from the nonperforated one, often in the case of the duodenum, from the posterior of the two kissing ulcers. Harrison and Cooper were able to demonstrate an open artery in one such case. I believe that gastric resection which removes the entire ulcer-bearing area and all sources of hemorrhage is indicated in these cases. A single experience of this kind is presented in Case 2.

CASE 2.—D. A., 48 years of age had had recurring ulcer symptoms for four years. He was admitted to the hospital five hours following perforation. For ten days prior to perforation he had had pain intractable to ulcer regime and four days previously had noted a tarry stool. At the onset of perforation he had vomited considerable coffee-ground material, felt faint, and had a large tarry stool; he later twice vomited blood. Examination revealed boardlike rigidity of the abdomen and acute tenderness throughout, with roentgenologic evidence of free air in the peritoneal cavity. The blood pressure of 100/70, the pulse of 110, and the marked pallor all suggested active hemorrhage. An immediate exploration was done and 1,000 c.c. of bank blood administered through needles in both arms simultaneously. There was diffuse but minor soiling of the peritoneum with grossly bloody fluid. On the lesser curvature about two inches distal to the cardio-esophageal junction, there was a small perforation which at the moment seemed to be sealed by a bloody fibrinous clot which was adherent to the anterior surface of the stomach about the perforation. A second ulcer slightly distal and on the posterior wall could be palpated. A biopsy was taken from the margin of the perforation for frozen section and this proved to be only inflammatory, with no evidence of carcinoma. The stomach contained a considerable quantity of blood. An antecolic Hofmeister type of resection was performed, 8 Gm. of sulfanilamide crystals were placed in the site of operation and abdominal wall, and the abdomen was closed without drainage. Following an uneventful convalescence, the patient

left the hospital in fourteen days. The gross specimen showed kissing ulcers high on the lesser curvature, the anterior one perforated, the posterior one penetrated to the serosa. The site of hemorrhage could not be definitely determined.

REPEATED OR RECURRENT ACUTE PERFORATION

Recurrent perforations are uncommon. In DeBakey's collection of 6,538 cases there were 74, or 1.1 per cent, reperforations. Davenport and Henry have each reported a case in which five reperforations occurred, and there are several recorded cases of three and four recurrent perforations. Patients in this category develop very acute ulcers which perforate with little or no warning. Because the records indicate that many of them have an ulcer diathesis and eventually require resection, there would seem to be adequate indication for an emergency resection at the time of the second perforation if performed under the favorable circumstances of early operation on a patient in good condition.

CASE 3.—G. B., 38 years of age, had had two previous perforations four years and ten months before, both treated by simple closure. He was admitted eight hours after the present or third perforation, and stated that for ten days he had vomited daily. Typical findings were presented, including roentgen evidence of free air in the abdomen.

At operation there was diffuse soiling but only a moderate amount of fluid. There was an astounding absence of adhesions from the previous perforations and operations. The stomach appeared to be dilated, and at the pylorus on the anterior wall there was a small perforation in the center of an indurated area which involved the entire circumference of the contiguous duodenum. The sites of previous perforations could not be identified.

Because the ulcer appeared to be acute, because it was the third one to perforate, and because there was evidence of pyloric obstruction, a subtotal anterior Polya gastrectomy was done. All fluid possible was aspirated from the peritoneal cavity, 10 Gm. of sulfanilamide crystals were placed around the site of operation and in the abdominal wall, and closure was effected with drainage of the wall only.

Convalescence was uncomplicated and the patient left the hospital in eleven days.

Examination of the specimen revealed, in addition to the perforated one, a penetrating kissing ulcer on the posterior wall and a small shallow prepyloric posterior ulcer.

PERFORATION ASSOCIATED WITH PYLORIC OBSTRUCTION

Perforated Jejunal Stoma Ulcer.—Only occasionally is the combination of fixed or permanent obstruction at the pylorus and acute free perforation encountered. Often the edema and induration about a perforated duodenal ulcer so narrows the lumen that many surgeons early in their experience have had much anxiety about restoration of patency following closure of the perforation, and not infrequently have been led to supplement closure with gastroenterostomy. Fortunately, the inflammatory process rapidly subsides and an adequate lumen is restored in all but a few cases. These may be designated as fixed in contradistinction to the apparent obstructions due to swelling. Fixed obstruction is the result of scarring incident to long-standing ulceration, often multiple ulcers. In these cases a by-pass must be provided and for this purpose gastroenterostomy is a poor second choice to resection.

In the patient whose history follows (Case 4), a gastroenterostomy had been performed and had proved inadequate. Not only had it failed to cure or prevent subsequent ulceration in the duodenum but also it had added a new source of trouble, an ulcer at the stoma which had perforated. This complication of ulceration in or about the stoma, or more often in the efferent loop of the jejunum, occurs not infrequently following gastrojejunostomy but only occasionally following subtotal gastrectomy. The incidence following gastrojejunostomy has been estimated at figures varying from 1.4 (Walton) to 34.0 (Lewisohn) per cent. There is also a wide difference of opinion regarding the frequency with which these ulcers perforate into the free peritoneal cavity. Liebein reported 30 perforations in 129 cases, an incidence of 23 per cent. Toland and Thompson who collected 93 cases, all that they were able to find in a search of the literature to 1936, estimated the incidence of perforation at less than 1 per cent.

The primary objective in the management of this emergency, as in the case of perforated gastric and duodenal ulcers, is the immediate survival and recovery. It would seem that simple closure is the simplest and therefore the safest method of accomplishing this objective. Curiously enough, this is not the case as judged by the evidence available in the literature. In the series collected by Toland and Thompson, simple suture of the perforation was carried out in 51 cases with 9 deaths, a mortality of 17.6 per cent. In 17 cases, the emergency was handled by subtotal gastrectomy with only 1 death, a mortality of only 5.8 per cent. Disconnection of the gastrojejunostomy restoring the normal sequential relation of the stomach and intestine was utilized in 4 cases with no deaths. Gastroenterostomy alone or in combination with other procedures was used in 7 cases with 2 deaths, a mortality of 28.5 per cent.

In only 1 case in this entire series was there reported the association of a perforated jejunal ulcer and fixed pyloric obstruction. As in my case, a subtotal gastric resection was done.

CASE 4.—J. J., 41 years of age, had had a posterior gastrojejunostomy two years previously for a duodenal ulcer which was intractable to therapy. He had been free of symptoms for one and one-half years, but during the past eight months symptoms had recurred and relief was obtained only with constant adherence to an ulcer regime. For two weeks there had been much pain at the umbilicus and in the back (about the first lumbar vertebra). It occasionally radiated into both testicles.

Four hours before admission the patient was seized with severe generalized abdominal pain and vomited only a small amount of bile-stained fluid. The clinical picture was typical of perforation. The blood studies revealed only a slight anemia, hemoglobin 12.5 Gm. and red blood count 4,000,500.

At operation, which was done immediately, diffuse and copious soiling and free gas were encountered, as were extensive adhesions between the abdominal wall, the omentum and stomach, and between the duodenum and liver. After retracting the transverse colon upward, the point of leakage was traced to a small perforation on the right anterior aspect of the gastrojejunal stoma. After adhesions were

freed, an ulcer was found on the superior aspect of the first portion of the duodenum and an apparent scar on the anterior aspect. The lumen appeared to be almost occluded at this point.

The anastomosis was taken down, the stomach subtotally resected, and a posterior full stoma anastomosis done.

As in the previous cases, sulfanilamide crystals were used and drainage was instituted for the abdominal wall only.

The patient had a very stormy convalescence as a result of atelectasis of the right lower lobe and what appeared to be peritonitis, followed on the eighth day by total wound disruption. However, he left the hospital in good general condition on the twenty-second day.

VERY EARLY PERFORATION IN THE VERY YOUNG

Under this heading are included the cases with insignificant soiling. The choice between resection and simple closure in this group is debatable and is influenced by individual factors such as the temperament and occupation of the patient and the inclinations and ability of the surgeon. In the hands of skilled surgeons, resection will be attended by little or no more primary mortality than simple closure, and the percentage of permanent cures will be much larger. The majority of individuals under 35 years of age do not remain free of ulcer symptoms following simple closure and in many instances the recurrent ulceration necessitates surgical intervention. Case 5 represents this group.

CASE 5.—D. B., 26 years of age, was admitted Dec. 8, 1943, two hours following perforation. He had had recurring ulcer symptoms for two years, which had always responded to ulcer therapy until the present episode which had lasted five days.

Immediately after eating his evening meal he was seized suddenly with severe general abdominal pain, worse in the epigastrium. Upon admission he presented the typical clinical picture of a patient with perforated ulcer, including radiographic evidence of free air in the peritoneal cavity.

At operation, which was performed immediately, there was diffuse soiling but only a moderate amount of fluid. On the anterior surface of the duodenum, just distal to the pylorus, there was a small perforation in the center of a wide area of induration. The duodenum appeared to be fixed posteriorly and there seemed to be palpable evidence of an ulcer on the posterior wall. In view of the two-year ulcer history, the athletic constitution of a man of 26 years, and a perforation of only two hours' duration, resection was performed as the procedure of choice. An anterior Polya type of operation was done; 8 Gm. of sulfanilamide crystals were placed in the abdomen and abdominal wall and a cigarette drain inserted to the peritoneum.

Convalescence was uneventful and the patient left the hospital twelve days after the operation.

CONCLUSIONS

1. From available statistical data it appears that subtotal gastric resection can be performed in the presence of diffuse soiling of the peritoneal cavity within twelve hours after the perforation of ulcerating lesions of the stomach, duodenum, and jejunum in good risk cases with a lower mortality than that obtained by simple closure with sutures. With few exceptions, resection results in permanent cure in contrast

to the high incidence of recurrent ulceration following simple closure of the perforations. This advantage is a justifiable consideration in the choice of operation by surgeons skilled in radical gastric surgery.

2. However, simple closure of perforations with sutures can be performed satisfactorily by surgeons with comparatively little experience, and subsequent radical therapy can be carried out under more favorable circumstances in the group of patients who develop recurrent ulcers with complications necessitating operation. For these reasons the immediate interests of most will be best served by simple closure.

3. There are, however, a few cases in which emergency primary resection is the operation of choice or has advantages that make it almost imperative. In the latter group are: (a) perforated resectable carcinomas of the stomach, (b) perforated peptic ulcers with simultaneous hemorrhage, and (c) perforated peptic ulcers with fixed pyloric obstruction. (Gastroenterostomy is an inferior alternative.)

In the other group the choice between simple closure and resection is debatable but resection is a justifiable preference in experienced hands because it offers much more assurance of permanent cure. Constituting this group are: (a) perforated peptic ulcers with insignificant or only local soiling (local soiling occurs in all elective resections except those performed by the so-called closed aseptic technique), (b) recurrent perforations, and (c) very early perforations in the very young patients who are otherwise in excellent health. In this group the incidence of recurrence is very high, the risk from resection very small, and the need for a permanent cure and good health very important.

REFERENCES

1. Aird, I.: Perforation of Carcinoma of Stomach Into General Peritoneal Cavity, *Brit. J. Surg.* 22: 545, 1935.
2. Bisgard, J. D., and Overmiller, W.: Emergency Gastrectomy for Acute Perforation of Carcinoma of the Stomach, With Diffuse Soiling of the Free Peritoneal Cavity, *Ann. Surg.* 120: 526-530, 1944.
3. Black, J. M.: Perforated Gastric and Duodenal Ulcer. A Survey of 50 Consecutive Cases, *Brit. M. J.* 2: 290, 1933.
4. Brinton: Quoted by Jaisson.¹⁸
5. Casberg, M. A.: Perforation as Complication of Gastric Carcinoma, *Arch. Surg.* 41: 937-974, 1940.
6. Chavannaz, J., and Radoiévitich, S.: Perforation des Cancers Gastriques, *Rev. de Chir.* 66: 3, 1928.
7. Davenport, G. L.: Five Operations in 12 Years for Perforation, *J. A. M. A.* 97: 99, 1931.
8. DeBakey, M.: Acute Perforated Gastroduodenal Ulceration, *SURGERY* 8: 1028, 1940.
9. DeBakey, M.: Acute Perforated Gastroduodenal Ulceration, *SURGERY* 8: 852, 1940.
10. Ditrich: Quoted by Jaisson.¹⁸
11. Gerhardt, F.: Experience With Treatment of Perforating Gastric and Duodenal Ulcer at the First Surgical Clinic of the University of Vienna Between 1919 and 1933, *Wien. klin. Wchnschr.* 49: 1389, 1936.
12. Gilmour, J., and Saint, J. H.: Acute Perforated Peptic Ulcer. A Review of 64 Cases, *Brit. J. Surg.* 20: 78, 1932-33.
13. Graham, R. R.: The Treatment of Perforated Duodenal Ulcers, *Surg., Gynec. & Obst.* 64: 235, 1937.
14. Von Haberer, H.: Zur Therapie akuter Geschwursperforationen des Magens und Duodenums in die freie Bauchhöhle, *Wien. klin. Wchnschr.* 32: 413, 1919.

15. Harrison, C., and Cooper, F. W., Jr.: Immediate and Late Results of Perforation of Peptic Ulcers, *Ann. Surg.* 116: 194-199, 1942.
16. Henry, C. K. P.: Recurrent Gastric Perforations, *Surg., Gynec. & Obst.* 32: 542, 1921.
17. Hromada, G., and Newman, S. S.: The Surgical Treatment of Perforated Ulcers of the Stomach and Duodenum, *Surg., Gynec. & Obst.* 35: 11, 1922.
18. Jaisson, A.: La perforation dans le Cancer de l'estomac; *Arch. de mal. de l'appar. digest.* 7: 384, 1913.
19. Judine, S.: A propos des gastrectomies d'esbolee pour ulcères perforés de l'estomac et du duodenum, *Mem. Acad. de chir.* 64: 419, 1938.
20. Judine, S.: Etude sur les ulcères gastriques et duodénaux perforés, *J. internat. de chir.* 4: 219, 1939.
21. Judine, S.: Partial Gastrectomies in Acute Perforated Peptic Ulcers, *Surg., Gynec. & Obst.* 64: 63, 1937.
22. Koehl, H.: Die Bewertung der Röntgenuntersuchung beim Magengeschwürsdurchbruch, *Zentralbl. f. Chir.* 60: 1518, 1933.
23. Laennec, R.: *Rev. Med. Franc. et Etrang.* 1: 379, 1824.
24. Lang: Quoted by Jaisson.¹⁸
25. Lewisohn, R.: The Frequency of Gastrojejunal Ulcers, *Surg., Gynec. & Obst.* 40: 70-76, 1925.
26. Lewisohn, R.: Secondary Gastric Resection for Perforated Gastrojejunal Ulcers With Peritonitis, *Ann. Surg.* 100: 1027-1030, 1934.
27. Liebein, U.: Das Ulcus jejunum und Ulcus gastrojejunale nach Gastroenterostomie, *Zentralbl. f. d. Grenzgeb. d. Med. u. chir.* 19: 64-162, 1917.
28. Marine, Usua: Tratamiento de la perforación aguda de estómago (con análisis de 150 observaciones) y resultados tardíos, *Rev. de cir. de Barcelona* 11: 115, 211, 317, 413, 1936; 12: 1, 35, 1936.
29. McNealy, R. W., and Hedin, R. F.: Perforation in Gastric Carcinoma, *Surg., Gynec. & Obst.* 67: S18-S82, 1938.
30. McNealy, R. W., and Hower, J. W.: Perforation in Peptic Ulcers, *J. Internat. Coll. Surgeons* 5: 115-124, 1942.
31. Mulleder, A., and Neuberger, J.: Zur Resektion beim perforierten Magen Duodenalulcus, *Wien. klin. Wchnschr.* 36: 743, 1923.
32. Nicholas, L.: Surgery of the Perforated Gastroduodenal Ulcer, *Arch. f. klin. Chir.* 191: 602, 1938.
33. Odelberg, A.: Primary Resection of the Stomach in Perforated Gastric and Duodenal Ulcers, *Acta chir. Scandinav.* 62: 159, 1927.
34. Parker, E. F.: The Late Results in Acute Perforated Peptic Ulcers Treated by Simple Suture, *SURGERY* 10: 49, 1941.
35. Paul, E.: Sur Frage nach dem Operationsverfahren beim perforierten Magen Duodenalgeschwür, *Deutsche Ztschr. f. Chir.* 172: 94, 1922.
36. Peters, K. O.: Bericht über primäre Resektionen wegen perforierter Magen und Zwölffingerdarmgeschwür, *Chirurg* 7: 78, 1935.
37. Pich, H.: Zur chirurgischen Beurteilung des Ulcus ventriculi perforatum und seiner Behandlungsmethoden, *Beitr. z. klin. Chir.* 159: 346, 1934.
38. Rieder, W.: Dauerergebnisse der primären Resektion beim perforierten Magen-Zwölffingerdarmgeschwür *Chirurg* 3: 884, 1931.
39. Sostegni, A.: Revisione di 52 casi di operati per perforazione gastrica, *Atti e mem. d. Soc. lombarda de chir.* 2: 1469, 1934.
40. Steiger, W.: Ein Beitrag zur Frage der Operationswahl beim perforierten Magen-Zwölffingerdarmgeschwür, *Wien. med. Wchnschr.* 85: 828, 1935.
41. Tilton, B. T.: Low Mortality of Early Operation for Perforated Gastric and Duodenal Ulcer, *Am. J. Surg.* 32: 238, 1936.
42. Toland, C. J., and Thompson, H. L.: Acute Perforation of Gastrojejunal Ulcers, *Ann. Surg.* 104: 827, 1936.
43. Toinon, L.: Des Complications Infectieuses des Cancers gastriques; perforations et fistules, Lyon, 1906.
44. Walton, A. J.: Failures of Gastric Surgery, *Lancet* 1: 893-897, 1934.
45. Winters, W. L., and Egan, S.: The Incidence of Hemorrhage Occurring With Perforation in Peptic Ulcer, *J. A. M. A.* 113: 2199, 1939.

SURVIVAL AFTER GASTRIC RESECTION IN CARCINOMA OF THE STOMACH

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THIS paper is presented as a review of the cases of carcinoma of the stomach in which the patients have been operated upon at the Highland-Alameda County Hospital. It is not the intention to study here all the patients with possible malignancies who have been admitted, treated or untreated, carcinoma diagnosed or suspected, only to look in retrospect at those patients who were considered operable after the abdomen was opened, had a pathologic diagnosis of the lesion, and have been duly followed through their succeeding years. Only by taking as a control group, cases so completed, can accurate and dependable information be given as to the results obtained at this hospital over this period of study.

In studying past cases of this type there could be an endless number of factors considered which, rightly, are weighed before the surgeon takes the patient to the operating room. And each of these factors, howsoever seemingly insignificant, could well have a major bearing on the cure or convalescence, but should each factor be discussed individually this would be an endless paper. So it has been assumed that if these patients have gone through major surgery, convalesced, and been closely watched over a period of years that such factors as their degree of anemia, weight loss, location of lesion, achlorhydria, and size as shown by film will not bear the significance to the patients in measuring the results obtained as the one which is to be taken into consideration—that of their longevity or survival rate.

From 1930 to 1944, an interval of fourteen years, exploratory laparotomies, contemplating palliative or curative procedures were performed on 463 patients with carcinoma of the stomach. From this total, there were 141 considered operable after the abdomen was opened. The follow-up clinic was able to carry through with a total of 96 cases, each having preoperative clinical and laboratory diagnosis of gastric malignancy, each confirmed by a pathologic diagnosis of the lesion removed, and each having autopsy at the time of death.

In studying this controll group of 96 on a follow-up basis, they have been divided into: (1) Operative deaths, (2) postoperative complications, (3) death under three years, (4) death under five years, (5) death under eight years, and (6) survival over eight years.

There were two patients who died during surgery; one death was attributed to hemorrhage and one was an anesthetic death, making

mortality during operation, 2.03 per cent. Of the fatal postoperative complications, three were latent hemorrhages, one subdiaphragmatic abscess, two generalized peritonitis, three postoperative pneumonias, or a total of nine, making 9.37 per cent mortality. Combining these two there was an operative risk of 11.39 per cent.

Of the 23 patients who did not survive over three years, not including the operative deaths, all had an extension of the lesion with metastasis. This group comprises 23.95 per cent of the original, which when added to those succumbing to surgery makes 35.34 per cent who failed to live over three years. For a little divergence and as a matter of comparison, it is interesting to note here that there were 28 patients seen in the hospital on whom a clinical and laboratory diagnosis of operable malignancy of the stomach had been made and who later came to autopsy at this institution. Of these patients, 100 per cent failed to live over three years. All 28 had refused surgery.

Still carrying this further, 36 patients, or 37.59 per cent, died in the three- to five-year interval, two from accidents, one from coronary disease, and one from cerebral accident. These five had no evidence of recurrence of their original lesion.

If the criteria of cure are to be based on a five-year curve, then there were 26 patients or 27.06 per cent, who survived. These resections appeared excellent, but 8 of these patients did not live over the eight-year period, 6 expiring from the recurrence of their original lesion and 2 from other pathologic conditions.

The next group narrows considerably. In this, there are a total of 18 patients who were alive and well for over eight years and symptom-free as far as their previous condition was concerned, a survival rate of 18.75 per cent over eight years. How do these results compare with those reported elsewhere? In 1942, the Mayo Clinic published an extensive study of carcinomas and other malignant lesions of the stomach, a series of 1,968 patients. In this publication, they reported a 28.9 per cent survival over five years, and 20.4 per cent over ten years, as against 27.06 per cent and 18.75 per cent for this institution.

To summarize, over an interval of fourteen years at this hospital, there were 141 patients with an established diagnosis of carcinoma of the stomach on whom gastric resection was performed. After five years, 27.06 per cent were alive, and 18.75 per cent had a survival rate over eight years. In contrast, there was a group of 28 in whom the diagnosis of gastric cancer had been established. This group of patients refused surgery and the mortality at the end of three years was 100 per cent.

THE CREATION OF A GASTRIC POUCH FOLLOWING TOTAL GASTRECTOMY

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THERE are still many problems confronting us in total gastrectomy, not only in the operative procedure but in the postoperative care as well. A problem which has attracted our attention recently perhaps has concerned others dealing with this type of surgery. That is, the inability of some patients following total gastrectomy and with an esophagojejunostomy to handle even small feedings without a feeling of fullness and discomfort. This can be a distressing symptom to the patient and of great concern to the surgeon since it presents a real problem as far as nutrient food intake is concerned.

Jordan,¹ of the Lahey Clinic, has reported a case of a woman who, after total gastrectomy and esophagojejunostomy, vomited and complained of substernal pain. This proved to be due to contracture of the anastomosis. These symptoms were relieved after dilatation of the anastomosis. I am not discussing the distress due to this complication but that due to the lack of physical space in the jejunum to handle a moderate-sized meal.

I would like to report here a case of similar symptoms, but one not due to stenosis or spasm of the esophagojejunal anastomosis. The symptoms were relieved by a secondary operation creating a pouch out of the afferent and efferent loops of jejunum.

CASE REPORT

A 57-year-old man was operated upon May 14, 1944, and a large peptic ulcer was found on the lesser curvature of the stomach involving the lower 1.3 cm. of the esophagus (Fig. 1). Because of the induration of the rest of the stomach and an associated gastritis it was decided that a total gastrectomy was the only answer to the problem.

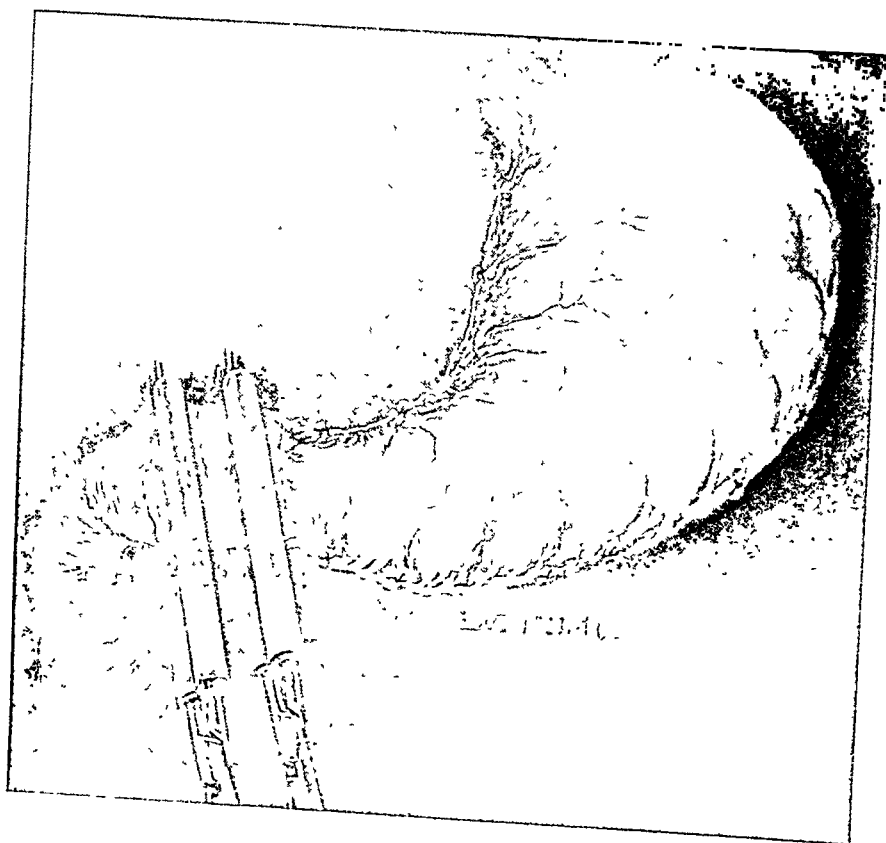
A total gastrectomy was done by first ligating the right and left gastric arteries and freeing them from the lesser curvature. The right and left gastric epiploic vessels were then ligated and their branches freed with the gastrocolic omentum from the greater curvature. The pylorus and duodenum were then mobilized. At this point the first portion of the duodenum was transected between clamps (Fig. 2). The distal stoma of the duodenum was closed with continuous chromic catgut No. 0 suture. This stump was then inverted with a linen purse-string suture, after which a row of interrupted sutures of linen were placed as seroserosal sutures. The closure of the duodenal stump is of paramount importance and cannot be stressed with too much emphasis (Fig. 3).

Received for publication, Dec. 11, 1944.

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Fig. 1.—Preoperative x-ray picture showing a small, penetrating ulcer high on the lesser curvature of the stomach.

Fig. 2.—Right and left gastric vessels and right and left gastric epiploic vessels have been ligated and separated. This diagrammatic sketch shows clamps in place for transection of duodenum.



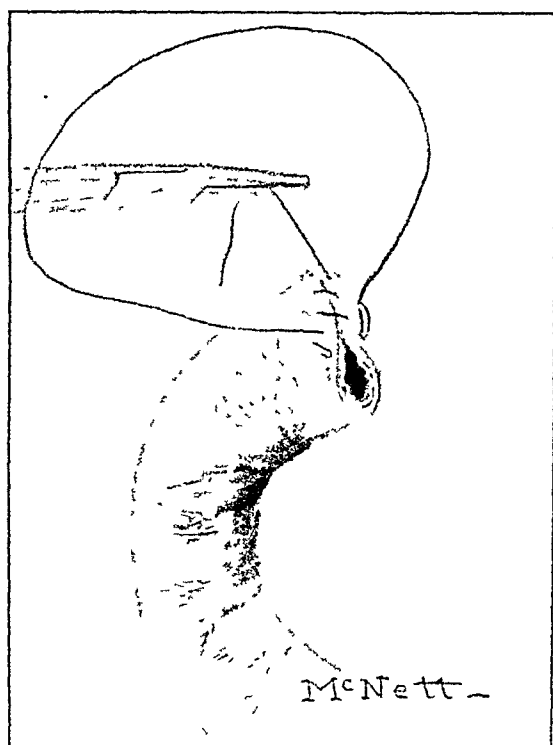


Fig. 3A.—Continuous suture for closure of duodenal stump

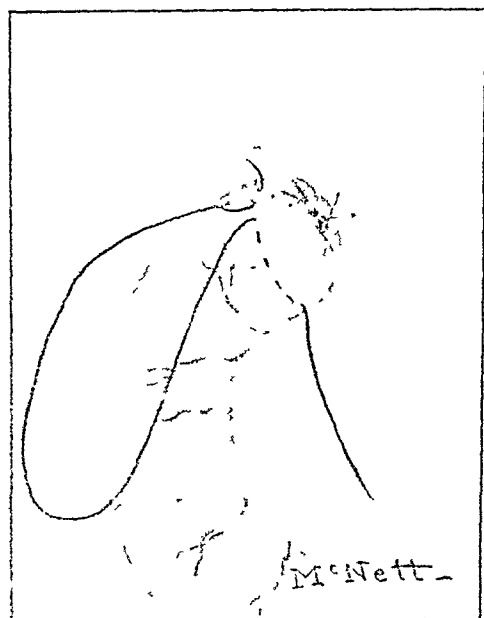
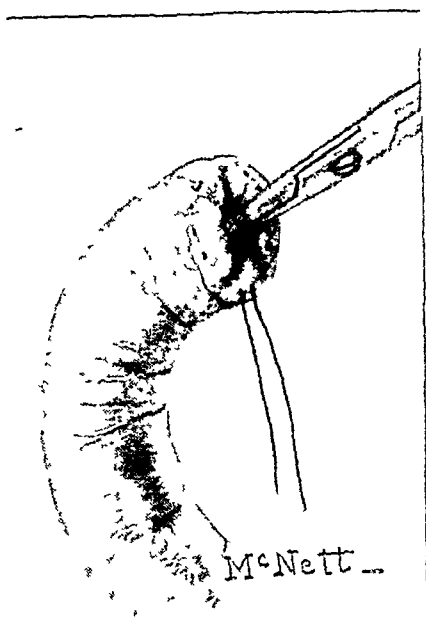


Fig. 3B —Stump closed with continuous suture, and purse-string suture being put in place.



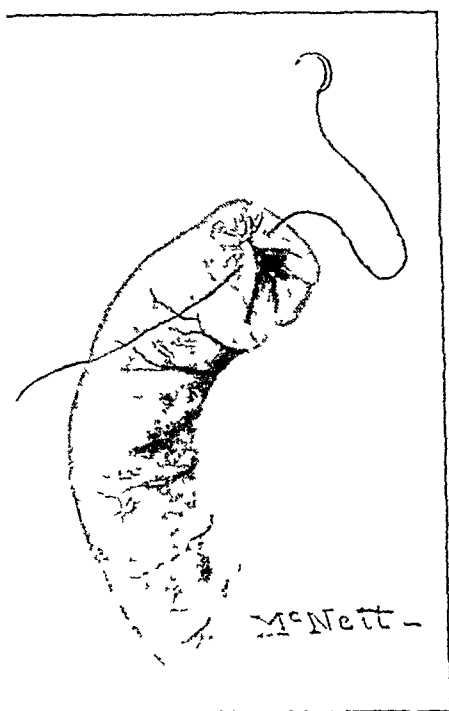
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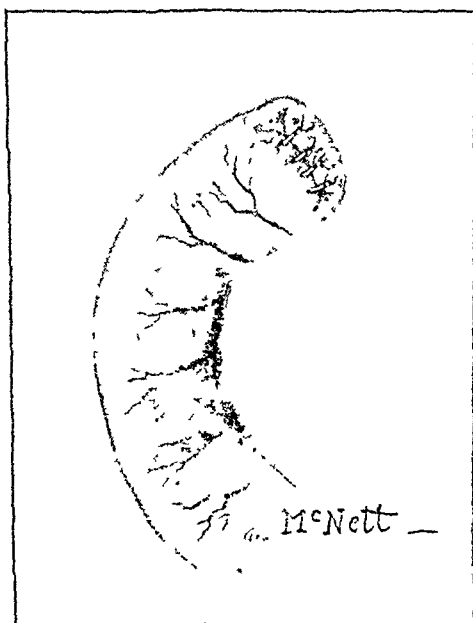
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Fig 3C—Burying of stump with purse-string suture

Fig 3D—Purse-string suture tied tightly, burying stump



E



F

Fig 3E—Interrupted linen seroserosal sutures are being placed

Fig 3F—Completion of stump closure

The reflection of the diaphragmatic peritoneum was then freed where it overlies the esophagus. May I point out here that the freeing of this peritoneal reflection allowed excellent mobilization of the esophagus. The anastomosis of the esophagus to the jejunum was done after the method of Lahey,² with a long jejunal loop brought up anterior to the transverse colon. It was felt wise here to amputate the great omentum to prevent drag on the afferent jejunal loop.



Fig. 4—The posterior suture line of the esophagus to the jejunum is in place with stomach retracted upward

In doing the anastomosis, it simplified the procedure to use the stomach to drag the esophagus downward and forward. A line of sutures was placed at the posterior suture line attaching the jejunum to the posterior aspect of the esophagus (Fig. 4). After this row of sutures were placed, the posterior wall of the esophagus just distal to the suture line was incised as was the jejunum. A second suture line (continuous No. 0 chromic catgut) was placed through the posterior layer of jejunum and the posterior wall of the esophagus (Fig. 5). After this the stomach and portion of the esophagus were removed by cutting through the anterior wall of the esophagus. The continuous suture was carried

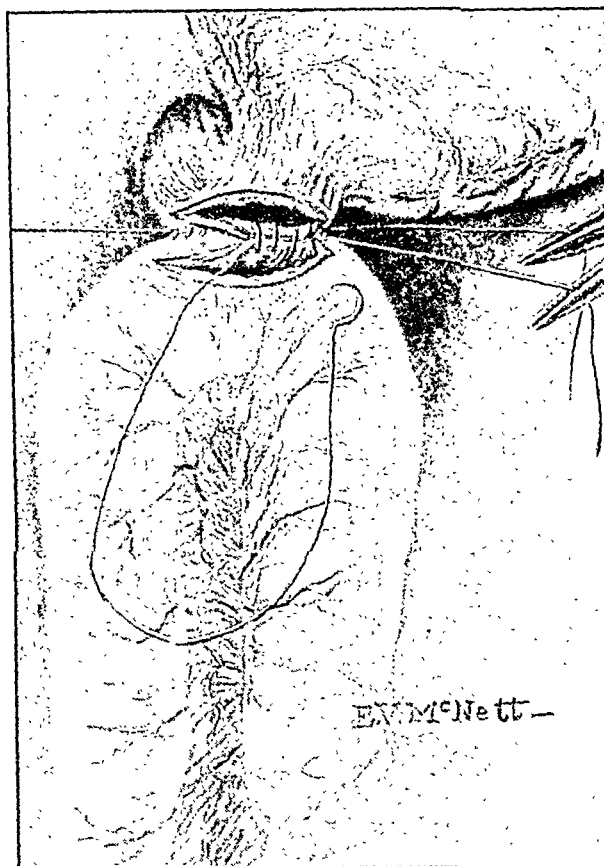
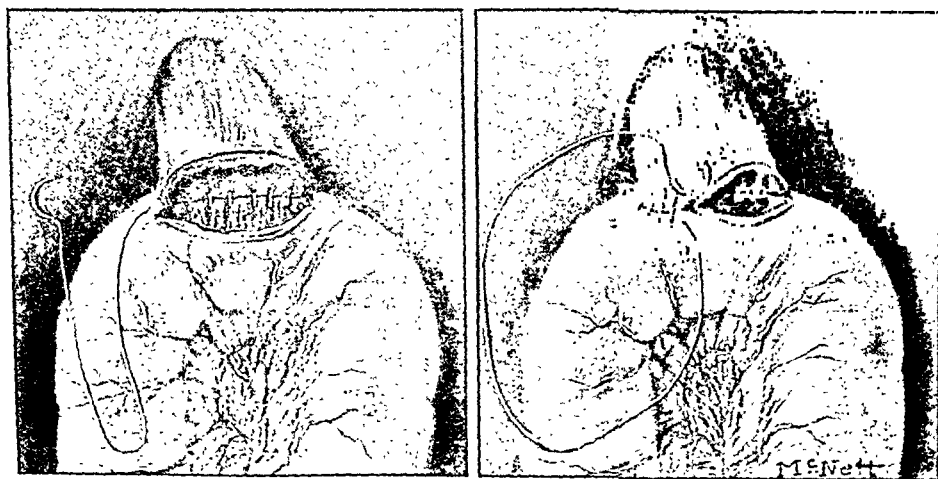


Fig. 5.—The beginning of the anastomosis to form the posterior wall of the esophagojejunostomy. Stomach is still being used for traction of the esophagus.



A.

B.

Fig. 6.—A, Completion of posterior closure of esophagojejunostomy. B, The beginning closure of anterior portion of anastomosis with the Lembert suture.



A.



B.

Fig. 7.—A, Completion of anterior closure of esophagojejunal anastomosis. B, One of four reinforcing sutures being put in place in the anastomosis.

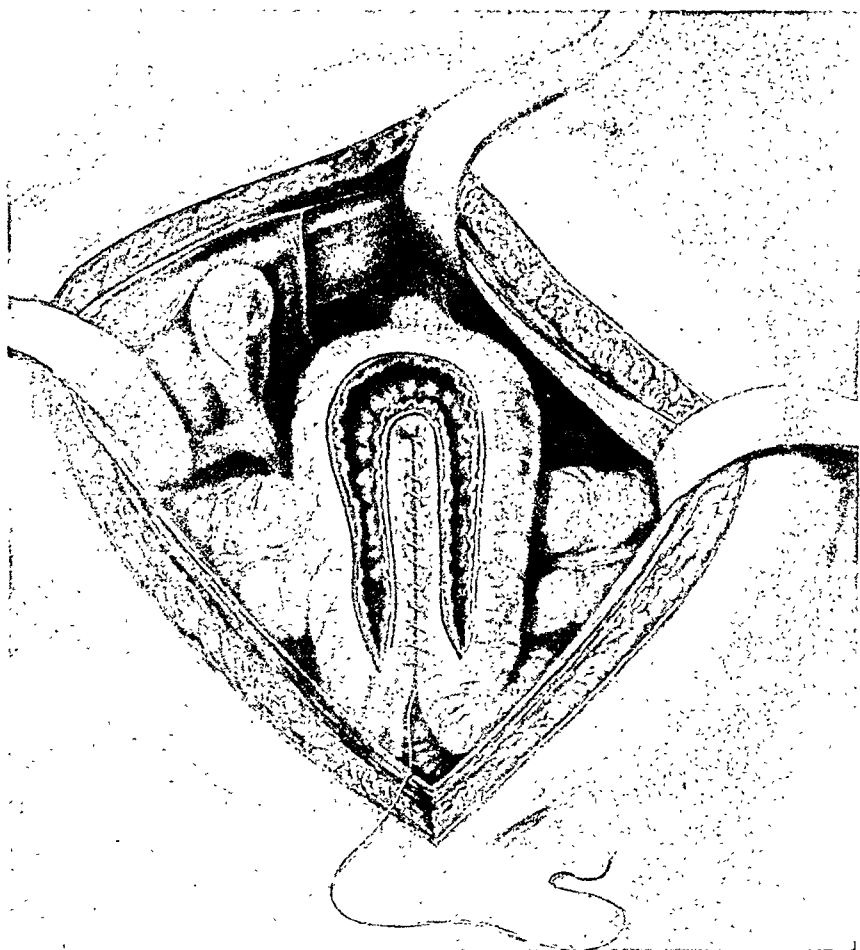


Fig. 8.—Seroserosal sutures between the afferent and efferent loops of jejunum in place and incision of the jejunum completed.

anteriorly to close the anterior wall of the jejunal opening to the anterior wall of the esophagus. Following this a second row of sutures was used to reinforce this line. Four interrupted sutures were placed at equal points around the anastomosis, through the muscular wall of the esophagus to the serosa of the jejunum for reinforcing the anastomosis and taking the drag off the anastomotic line (Figs. 6 and 7). Still another row of sutures was placed from the serosa of the jejunum to the diaphragmatic reflection of the peritoneum which was originally freed. A Jutte tube was passed down the esophagus and into the efferent loop of jejunum for a distance of about 8 cm. This was to be used for postoperative feeding. The abdomen was then closed in layers without drainage.

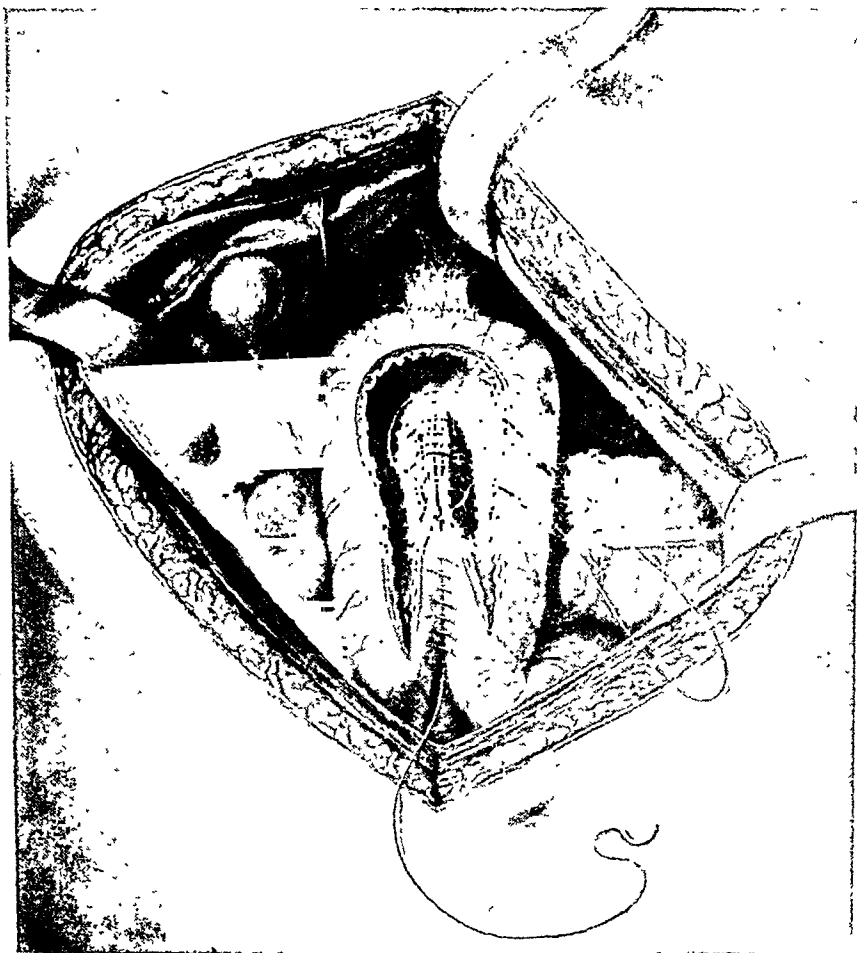


Fig. 9.—The beginning of the suture through the six layers of the two loops of jejunum forming the posterior wall of the pouch.

The feedings were carried on at 30 Gtt. per minute. These feedings alternated 500 c.c. of Karo syrup in water and 500 c.c. of predigested beef.* In twenty-four hours 1,000 c.c. of each mixture was given. This totaled 1,770 calories. Liquids were started by mouth and the feeding tube removed on the sixth day.

*Select one-half pound of beef. Remove everything that is not clear meat. Chop fine. Put in pint fruit jar and add one cup of cold water and five drops of dilute hydrochloric acid. Stir and set in refrigerator or any cool place to digest for two hours. Strain, season, and serve in drip bottle.

Soft diet was started on the seventeenth postoperative day on a six-feeding basis. The patient complained of fullness and distress after eating. A barium x-ray picture was made which showed the anastomosis to be normal sized and functioning. The complaint and symptoms of distress continued, and on the twenty-eighth postoperative day it was decided to reoperate and make a pouch out of the afferent and efferent loops of jejunum.

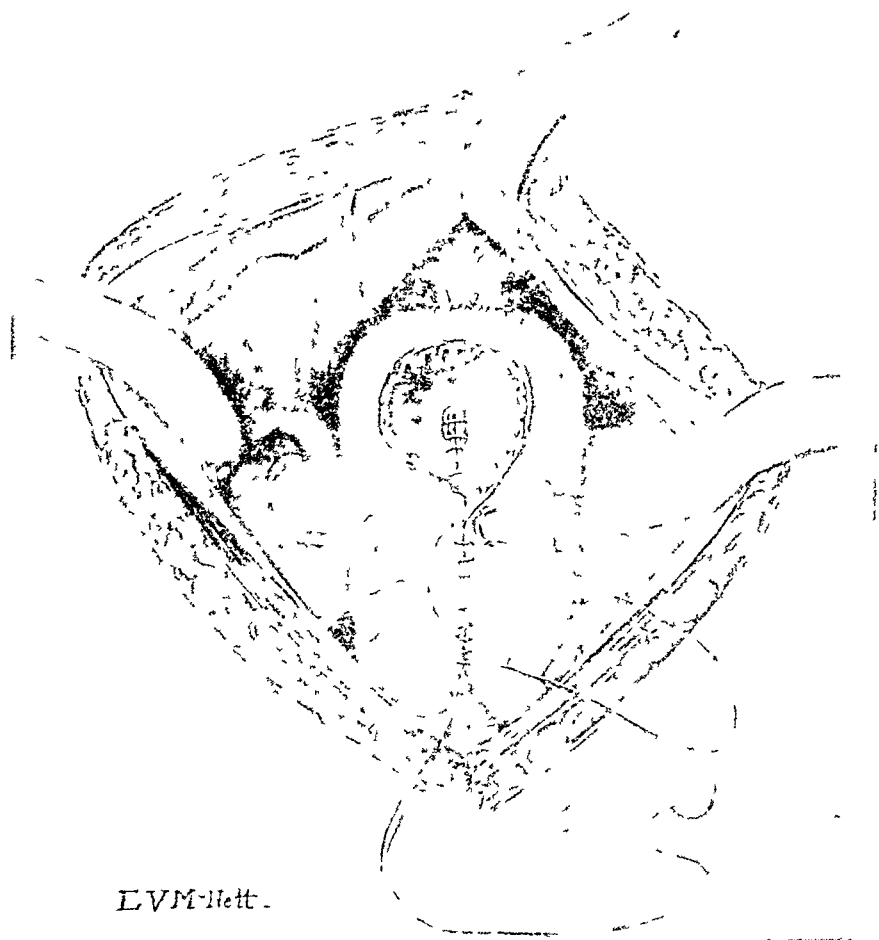


Fig 10—The start of the closure of the anterior wall of the pouch by a Lambert suture. The original seroserosal suture is seen in the lower portion.

I reoperated upon the patient through the same upper right rectus incision. The peritoneum was opened and the anastomosis was examined. It was found to be patulous and one finger in diameter. The afferent and efferent loops of jejunum were brought next to each other. Beginning at the upper angle formed by these two loops, a seroserosal suture was started about 1.5 cm. from the mesenteric attachment. This suture was carried down, suturing the afferent and efferent loops together for a distance of 8 cm. (Fig. 8). An incision was then made through all three layers of the afferent loop near the seroserosal suture line. This incision was carried upward on the afferent loop to the angle of the jejunum near the anastomosis, across this angle and down the efferent loop to the lower end of the seroserosal suture (Fig. 9). The medial walls of the afferent and

efficient loops of jejunum were then sutured together, starting at the upper angle with a continuous chromic No. 0 catgut. This suture completed the posterior wall of the pouch. When the lower angle of the incision was reached the suture was continued as a Lambert suture, bringing together the lateral wall of the incision in the afferent loop to the lateral wall of the incision in the efferent loop (Fig. 10). When this suture was completed the original seroserosal suture was continued up the anterior wall overlying the Lambert suture line and completing the closure of the anterior wall of the pouch (Fig. 11). The abdomen was then closed in layers.

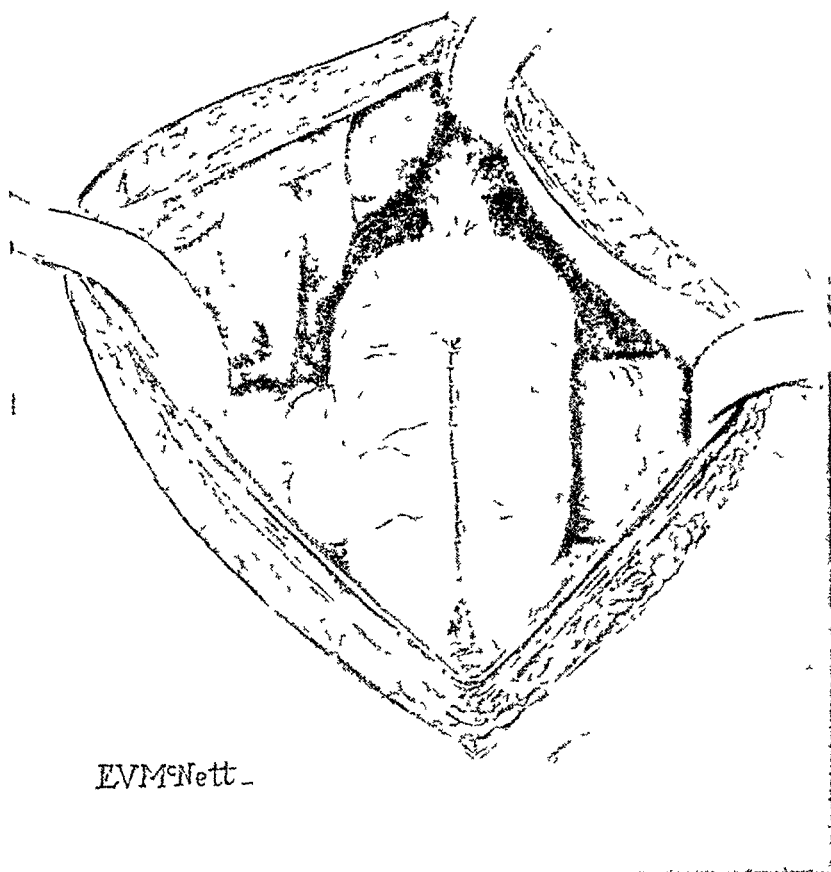


Fig 11—The completion of the seroserosal suture up the anterior wall of the two anastomosed loops of jejunum, completing the formation of the pouch

The postoperative course of the patient was uneventful. Tube feedings were started through a Jutte tube which had been passed down the esophagus, through the pouch, and down the efferent loop of jejunum. Mouth feedings of liquids were started on the third postoperative day, when the feeding tube was removed. Soft diet was started on the eighth postoperative day and light diet on the fourteenth day. The patient did well and had no complaints. X-ray on the seventeenth day after the pouch was made showed it to be working fine. The patient was discharged the following day (Fig. 12).

A fractional test meal of the pouch contents showed no free hydrochloric acid. The total acidity was 22.24. Serum protein varied from 5.75 to 6.29 per cent.

Six months after operation the patient's hemoglobin was 91 per cent, red blood cells 5,220,000, serum protein 6.12, and blood chlorides 444 mg. per cent. A fractional test meal showed no free hydrochloric acid, no free lactic acid, and a total acidity of 2.5. The patient's only complaint was a restricted diet. He had gained fifteen pounds since operation and was on a full diet of three meals per day. Complete mastication of food was stressed as the most important thing to future health. At that time he was working in a war plant doing a full forty-eight hour a week job.

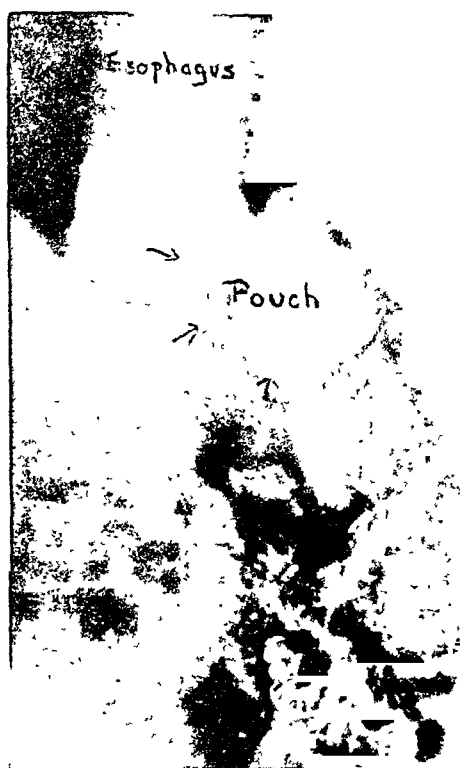


Fig. 12.—X-ray of patient before discharge, showing pouch filled with barium.

I have since operated upon a 66-year-old woman for carcinoma of the fundus of the stomach. In this case I did a total gastrectomy after the Lahey method and at the same time made a pouch of the afferent and efferent loops, all at one stage. This patient made an excellent recovery and never had a complaint of distress or fullness on eating.

The technique for this pouch operation was somewhat similar in manner to the Finney³ gastroduodenostomy except that instead of using stomach and duodenum the anastomosis was made between the two loops of jejunum.

Another great aid in gastric surgery is the recommendation by Allen and Donaldson⁴ of the use of jejunostomy for decompression and feeding. In the total gastrectomized patient the use of Allen's method

of jejunostomy for feeding is ideal. In the subtotal gastrectomized patient both the decompression tube and the feeding tube are of tremendous importance to the safety and the comfort of the patient.

It seems that in some cases, at least, the creation of a gastric pouch is of definite benefit to the total gastrectomized patient. The pouch may be created by using the afferent and efferent loops of jejunum with very little difficulty, and may be done as a second stage procedure or at the original resection.

REFERENCES

1. Jordan, Sara M.: Medical Aspect of Cancer of the Stomach, J. A. M. A. 112: 618-623, 1939.
2. Lahey, F. H., and Marshall, S. F.: Technic of Subtotal Gastrectomy for Ulcer, Surg., Gynec. & Obst. 69: 498-507, 1939.
3. Finney, J. M. T.: Gastroduodenostomy, Operative Surgery (Bickham), Vol. 4, Philadelphia, 1924, W. B. Saunders Company, pp. 288-289.
4. Allen, Arthur W., and Donaldson, Gordon: Jejunostomy for Decompression of the Postoperative Stomach, SURGERY 15: 565-568, 1914.

PROLONGED SPINAL ANESTHESIA

DESCRIPTION OF A SIMPLIFIED TECHNIQUE FOR NUPERCARNE

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SINCE the introduction of subarachnoid block by Bier in 1898, there has been a ceaseless search for a technique which would provide prolonged as well as controllable anesthesia. Prolonged spinal anesthesia may be obtained in one of two ways: (1) by the continuous or serial technique; (2) by a single intrathecal injection of a long-acting local anesthetic drug. The most recent advancement in the direction of prolonged anesthesia has been the introduction of the "continuous spinal" technique by Lemmon.¹ Although the continuous technique has been widely publicized and acclaimed, it is far from ideal. The thick cumbersome mattress, the frequent dislodgment of the indwelling needle, the difficulty and uncertainty of establishing anesthesia in the desired segment, and the possibility of injury to the intraspinal structures by either the needle or repeated doses of the drug are objectionable features. Besides, its induction is time consuming. The modified technique suggested by Tuohy,² employing the indwelling catheter, eliminates the mattress and failures due to dislodgment of the needle, but increases possibility of fistulas, infection, and leakage of spinal fluid.

Although many drugs have been employed for spinal anesthesia, few yield prolonged action by the single injection method. Pontocaine and nupercaine are the two currently available agents most useful in this respect. Pontocaine has enjoyed popularity since Sise³ advocated its administration with glucose. The addition of glucose to solutions of local anesthetic drugs causes them to be hyperbaric or heavier than spinal fluid. The effects of gravity may then be utilized to extend anesthesia to the desired spinal segment by tilting the patient during the induction period. Exact localization of the drug is possible because cephalad diffusion of the pontocaine in the spinal canal appears to be minimized by the glucose. When employed by capable individuals in suitable subjects, the pontocaine-glucose technique yields excellent results and is entirely satisfactory. Although pontocaine is satisfactory for most operations, nupercaine is preferred when the procedure is to last more than two hours.

The various methods advocated for the administration of nupercaine are not as simple as the technique described by Sise for pontocaine. The method described by Jones⁴ is the most popular at the present time. In this technique, a relatively large volume of a hypobaric solu-

tion is introduced into the subarachnoid space. During the induction period, it is necessary to turn the subject face downward and tilt the table so that the head remains dependent for approximately ten minutes. The prone position insures a caudad, rather than cephalad, movement of the solution. It also allows the posterior root filaments to come into contact with the solution so that satisfactory sensory anesthesia is secured. The results obtained by Jones' technique are frequently disappointing because diffusion of the nupercaine is an uncontrollable factor. Satisfactory localization of the drug at the desired segment is secured with difficulty because there is no logical basis for determining the volume of solution required. Severe circulatory disturbances often follow the shift from the prone to the supine position after anesthesia is established. Besides, the induction is time consuming. The technique described by Wilson⁵ also requires the use of a comparatively large volume of dilute solution. The subject remains in the upright posture during the injection so that upward diffusion is assured. This technique is characterized by lack of controllability and is fraught with considerable danger.

There is no reason why nupercaine cannot be substituted for pontocaine in the glucose technique. Pontocaine and nupercaine are used in approximately the same quantities as far as weight is concerned. Besides, both drugs behave similarly as far as solubility, stability, and pH of aqueous solution are concerned. The prolonged action of nupercaine could thus be secured with the precision and simplicity allowed by the pontocaine-glucose technique.

The use of hyperbaric solutions of nupercaine has been described in previous reports. Silverton⁶ employed a solution of $\frac{1}{2}$ per cent nupercaine in 6 per cent glucose. He relied principally upon barbotage to force the drug to the desired segment. Sankey and Whitacre⁷ add glucose to the solution described by Jones. The height of anesthesia is controlled largely by the displacement afforded by the large volume of fluid, rather than by the effects of gravity.

The technique we have developed is simpler than any previously described for nupercaine. Furthermore, it is rapidly executed and is reasonably controllable. The results are little influenced by wide variations in such intrinsic factors as length and diameter of the cord, size of subarachnoid space, or body weight. There are six extrinsic factors which may affect the extent and intensity of spinal anesthesia. These are volume of solution injected, specific gravity of solution, rate of injection, dose of drug, site of injection, and position of the patient after injection of drug. The fewer the variations, the simpler the technique. In this technique all factors are fixed with the exception of position of the patient. The patient is tilted immediately after the injection and progress of anesthesia is followed from moment to moment until it is at the desired segment, at which time cephalad ascent may be terminated by leveling the table. If one desires, the drug may

be confined to the lowest spinal segments and anesthesia so localized that it involves the perineum only and not the legs. On the other hand, anesthesia may be established at the cervical segments if one so desires.

Nupercaine (also known as percaine) differs in a number of respects from procaine, pontocaine, and related anesthetic drugs. The majority of local anesthetic drugs are esters of complex alcohols. Nupercaine is a substituted amide derived from quinoline and is not an ester. The impression that nupercaine is derived from quinine is not correct. Quinine is a cupreine. Cupreines are complex structures which contain not only a quinoline nucleus but also other groups and radicals as well. Nupercaine is a weak base which forms salts when neutralized by mineral acids. The base is easily precipitated from aqueous solutions of its salts by alkalis and basic salts.

TECHNIQUE

The preparation employed for this technique consists of $\frac{1}{2}$ per cent nupercaine hydrochloride dissolved in a phosphate buffer and saline solution. Each cubic centimeter contains 5 mg. of the drug. The volume of solution containing the estimated dose of nupercaine is thoroughly mixed with an equal volume of 10 per cent glucose in physiologic saline or distilled water. The resulting volume of solution, even when the maximum dose is employed, is relatively small. Variations in volume due to variations in dosage used are relatively insignificant. The mixture is injected into the subarachnoid space through a 20 or 22 gauge needle as rapidly as gentle pressure on the plunger permits without barbotage. Although the lateral prone position is preferred in performing the block, the upright sitting posture may be employed if one so desires. The spinal puncture is performed at the level of the third lumbar interspace for anesthesia above the costal margin and at the level of the fourth lumbar interspace when less extensive anesthesia is required. Immediately following the injection, the patient is placed on his back and the operating table is tilted in a Trendelenburg position. The angle varies with the height of the anesthesia desired. The head is flexed as sharply as possible upon the thorax by supporting it upon a pillow which has been doubled upon itself (Fig. 1). Unless this precaution is rigidly observed, the mixture may ascend into the cervical region and cause respiratory failure by affecting the phrenic nerves. Generally, within fifteen to twenty seconds the subject notes a feeling of numbness in the lower extremities. In contrast to the behavior of the shorter-acting drugs such as procaine, metycaine, monocaine, and others which seem to act almost immediately, the onset of anesthesia is delayed when nupercaine or pontocaine is employed. Occasionally, ten minutes or more may be required for establishment of complete anesthesia by nupercaine introduced intrathecally. However, hypalgesia, which always precedes anesthesia, ensues immedi-

ately. Consequently, when performing the sensory examination to establish the level of anesthesia, one does not seek the areas of complete insensibility, but instead those of hypalgesia or diminished sensation. An area of complete anesthesia will be revealed over the anterior surface of the thighs within approximately one minute after completion of the injection. One should always test sensation gently with a sharp instrument. As the examining instrument is advanced cephalad, an area of hypalgesia is encountered which appears to diminish in intensity and merges into a totally unanesthetized area over the upper part of the body. The line of demarcation between the hypalgesic and unanesthetized area is reasonably sharp and well defined. When the line of demarcation lies in the dermatome in which anesthesia is desired, the ascent of the drug is terminated by promptly

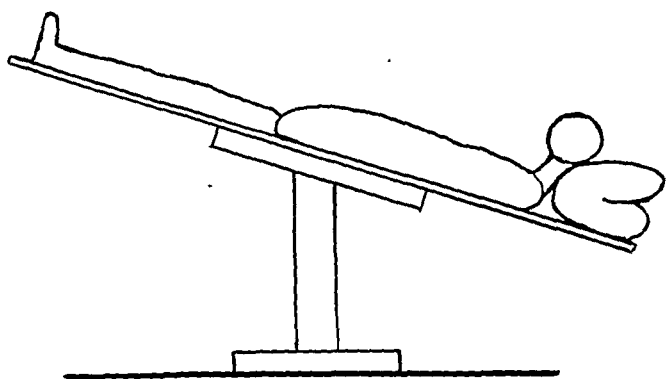


Fig. 1.—Method of acutely flexing the head to prevent movement of the drug into the cervical portion of the spinal canal.

readjusting the operating table to the horizontal position. The hypalgesic areas in due time become completely anesthetic. There appears to be little or no tendency for anesthesia to creep beyond a given level once it is established at that level. Under no circumstances does one rely upon the line of demarcation between the zone of complete anesthesia and the zone of hypalgesia for establishing the level. If one relies upon anesthesia rather than hypalgesia in the sensory examination, anesthesia may extend far above the desired spinal segment.

The time the patient remains in the inclined position varies for each individual case. As few as thirty seconds or as many as three minutes may be required for the drug to reach the desired segments. So many variable factors modify the cephalad progress of the drug that no fixed time interval can be stated. The degree of inclination of the operating table likewise cannot be standardized, but must be adjusted to suit the needs of each individual patient. For upper abdominal surgery the lower seven thoracic segments must be anesthetized. To secure this extent of anesthesia, the inclination must be steep—approximately twenty degrees. One should be prepared to brace the shoulders imme-

diately after the solution is injected. If the operating table is inclined at an angle of less than twenty degrees, the drug may not reach the thoracic spinal roots and unsatisfactory anesthesia results. For the sake of safety, the progress of the drug in the cephalad direction should be followed by almost continuous sensory examinations as long as the patient is in the inclined position. The operating table should be restored to the horizontal position immediately if the drug appears to advance rapidly or if anesthesia advances beyond the desired sensory segments. If the drug appears to involve the upper thoracic or lower cervical segments, the operating table should be restored to the horizontal or placed in the reversed Trendelenburg position at an angle of 5 to 10 degrees. The reversed Trendelenburg position not only terminates the upward advance of the drug, but favors a caudad regression of the solution. For best results, it is imperative that there be as little delay as possible in inclining the table when the intrathecal injection is completed. Failure to obtain satisfactory anesthesia for upper abdominal surgery is frequently due to delays in inclining the table promptly. The operating table need not be as steeply inclined when anesthesia below the costal margin is sought. An angle of 10 to 15 degrees is usually sufficient. To obtain "low" spinal anesthesia, that is, anesthesia of the perineum or extremities, the operating table should be tilted immediately to the Trendelenburg position at an angle of approximately 10 degrees for five to ten seconds. It is then returned to the horizontal position if anesthesia over the hypogastric area is desired and placed in the dependent position at an angle of 5 degrees if anesthesia is to be confined to the extremities. Failure to tilt the table to the Trendelenburg position immediately after the injection is completed may result in uneven or "spotty" anesthesia and incomplete muscular relaxation. It is obvious that this technique cannot be successfully employed if a table which is easily tilted is not available.

It is a well-established pharmacologic fact that the sensory fibers of a mixed nerve are the first to be affected by a local anesthetic drug, the autonomic fibers next, and the motor fibers last. For several minutes after establishment of sensory anesthesia by this technique, motor power remains unchanged or is mildly depressed. Motor paralysis is rarely completely established in less than five minutes. The degree of motor paralysis varies in the different spinal segments, depending upon the concentration of drug in each segment. In the thoracic region where the concentration of drug is obviously less than at the site of puncture, more sensory fibers are involved than motor. Muscle relaxation, therefore, is incomplete or absent. At the site of injection and throughout the lumbar region, the concentration of drug is greater and all types of nerve components are affected. Anesthesia, therefore, is complete. The concentration of drug in the upper spinal segments may be increased by increasing the total amount of drug injected.

Motor anesthesia becomes more extensive. It is obvious, then, that muscle relaxation is controlled by varying the quantity of drug. The dosage, therefore, depends upon intensity and extent of anesthesia desired. For upper abdominal surgery, 12 to 15 mg. of nupercaine yield satisfactory sensory and motor anesthesia. For anesthesia below the costal margin, 7 to 10 mg. are ample; for surgery of the extremities, $2\frac{1}{2}$ to 5 mg. are sufficient. In the upper age groups, the lower limits of dose ranges should be employed. Formulas such as milligrams per pound of body weight, milligrams per centimeters of length of the vertebral column and the like have proved to be no guide to the amount of drug required. The intrinsic factors, such as length and diameter of the cord, and volume of the spinal subarachnoid space, are so variable that in using a drug which is potent and which is used in relatively small quantities, these rules of dosages are valueless.

The time-honored custom of mixing the drug with cerebrospinal fluid was dispensed with in this technique for two reasons: (1) Spinal fluid, which has a pH of 7.4, is sufficiently alkaline to cause a precipitation of nupercaine base from aqueous solutions of the hydrochloride. Unsatisfactory anesthesia results if one employs a solution in which flocculation has appeared. Laboratory studies suggest that glucose prevents precipitation of the free base when solutions of salts of local anesthetic drugs are injected into the subarachnoid space.⁸ (2) The solution may be prepared in advance of the lumbar puncture and injected immediately upon completion of the puncture. Failures due to dislodgment of the needle or shifting of the patient's position while solutions are being prepared are thus averted.

Ten to fifteen minutes should be allowed to elapse after injection of the solution before changes in posture are attempted. Trendelenburg, prone, lithotomy, and other positions necessary for completing the operation may then be employed with safety. After ten minutes have elapsed, the glucose diffuses throughout the spinal fluid and no longer causes the drug to shift about in the subarachnoid space.

RESULTS

Anesthesia induced by this technique was employed for 800 consecutive surgical procedures of all types. In 9.5 per cent of the cases, anesthesia extended to or beyond the fifth thoracic segment; in 59 per cent of the cases, it was established between the twelfth and ninth thoracic segment; and in the remainder of the cases, it was confined exclusively to the lumbar and sacral segments. Satisfactory anesthesia was obtained in all but ten subjects. In these, failure was due to unsatisfactory lumbar puncture. In thirteen subjects undergoing abdominal surgery, sensory anesthesia was satisfactory, but motor anesthesia of the lower extremities was incomplete. The abdominal muscles, however, were well relaxed and there was no interference with the

progress of the operation. It is felt that this incomplete motor paralysis was due to a delay in tilting the operating table following the induction of the solution.

Duration of anesthesia ranged from two to three hours in 0.8 per cent of the cases, three to four in 98 per cent, four to six in 1.2 per cent of the cases. The average duration of anesthesia was three and one-half hours.

Although it is difficult to make comparisons, the general impression gained was that hypotension was no more severe or more prevalent with nupercaine than in spinal anesthesia with other drugs. It appeared, as one would expect, more frequently in "high" spinal than in "low" spinal anesthetics. In most instances, it appeared immediately following or shortly after induction of anesthesia. Vasopressor drugs such as ephedrine, neosynephrin, or enethyl were effective restoratives in every instance in which it occurred. Nausea, vomiting, and retching were observed in approximately 1 per cent of the cases. In each instance these reactions were observed during upper abdominal explorations, and appeared to be due to traction upon the viscera. Restlessness, which appears in the majority of subjects undergoing prolonged operations under spinal anesthesia, was controlled by the use of sedatives. A combination of morphine sulfate gr. $\frac{1}{6}$ to $\frac{1}{8}$, and scopolamine gr. $\frac{1}{150}$ to $\frac{1}{200}$ (a ratio of 25 parts morphine to 1 part scopolamine), intravenously, was found to be particularly useful for this purpose.

The technique was employed for anesthesia for abdominoperineal resection in seven subjects. This is noteworthy because the hypobaric solution of nupercaine has not proved satisfactory for this type of operation. The abdominal anesthesia is satisfactory, but the sacral and lower lumbar segments frequently are not completely anesthetized. This discrepancy has not been adequately explained. To insure satisfactory anesthesia in the perineal area, the injection may be made while the patient is in the upright sitting position. The patient is then tilted and managed as previously described.

DISCUSSION

In determining the value of a local anesthetic drug for spinal anesthesia, one must base its merits upon potency, systemic toxicity, and local toxicity. Objections are frequently raised to nupercaine for spinal anesthesia on the grounds that it is more toxic than many of the currently employed local anesthetic drugs. Nupercaine is both more toxic and more potent than procaine and similar agents. Too often toxicity is confused with potency. The comparative systemic toxicity of local anesthetic drugs for man is difficult to estimate. Studies in animals indicate that nupercaine is approximately eight to ten times more toxic than procaine.⁹ On the other hand, it is twelve to fifteen times more potent than procaine. One must bear in mind

that potency and toxicity do not necessarily parallel each other. One milligram is theoretically equivalent in action to approximately 15 mg. of procaine. The amount of nupercaine required for the same degree of anesthesia yielded by procaine is considerably less. Therefore, though nupercaine possesses a greater absolute toxicity, its relative toxicity approximates that of procaine.

The more potent one drug is, compared to another, the greater the intensity of anesthesia it will cause when used in equivalent amounts. Therefore, the intensity of anesthesia may be controlled by varying the dose, regardless of the agent employed. The severity of the physiologic disturbances which accompany spinal anesthesia depends upon the intensity of anesthesia. The greater the number of dermatomes affected by the drug and the greater the number of sensory, motor, and autonomic components which are involved in a spinal segment, the more intense will be the anesthesia. Physiologic disturbances appear during spinal block, regardless of the drug employed, if the amount injected is sufficient to produce extensive anesthesia. The most distressing physiologic disturbance accompanying spinal anesthesia is hypotension. Although there is no agreement regarding the mechanism causing it, it is probably the result of a combination of factors, all of which are dependent upon the extent of the resulting paralysis. The relaxation of the muscles of the extremities, the paralysis of the abdominal muscles, the diminution of ventilation from paresis of the intercostal muscles, and the paralysis of the sympathetic nervous system, all contribute to the peripheral circulatory failure and cause pooling of the blood in the venules and capillaries. Relatively small amounts of nupercaine, by yielding extensive anesthesia, may cause marked physiologic disturbances, particularly when the anesthesia affects many spinal segments. Hypotension is a manifestation of potency rather than toxicity. A toxic reaction is due to a high concentration of drug in the blood. Such reactions may be due to accidental intravascular injections or rapid absorption of the drug into the blood stream. Excitement, nausea, vomiting, convulsions, and ultimately respiratory and circulatory failure are the usual symptoms of toxicity. Local anesthetic drugs cause, at first, a marked stimulation of the central nervous system. If the overdosage is massive, depression and paralysis quickly follow. Toxic reactions are not benefited by vasopressor substances, oxygen, and other supportive measures so useful for the relief of hypotension. Fortunately, toxic reactions are rare in spinal anesthesia.

Considerable disagreement exists concerning the reversibility or "local toxicity" of various local anesthetic drugs administered intrathecally. Neurologic complications ascribable to changes produced in the intraspinal elements by the local action of the drug have been reported following the use of most of the currently employed local anesthetic drugs. It is almost impossible to draw any conclusion regarding the

relative merits of one agent over another from the isolated case reports which appear in the literature. Systematic studies of this problem have not been attempted and are few because of the difficulty in studying the spinal cord in routine autopsies. A considerable amount of data of an experimental nature exists, however. Recently Co Tui and his co-workers,¹⁰ in comparing the effects of procaine, nupercaine, and monocaine in cats and rabbits, found that slight transitory changes occur in the cords of these animals when therapeutically equivalent doses of drugs are employed. The quantity of nupercaine required to produce the same anesthetic effect as the pharmacologic equivalent of procaine produced the same degree of histologic change as procaine. The changes lasted for the same period of time with each drug. However, when the minimum lethal dose was employed, the changes produced by nupercaine were more intense and not reversible. On this basis, one would assume that the local toxicity of nupercaine is no greater than a therapeutic equivalent of procaine. No instance of a neurologic complication was observed in any case in this series during the period of hospitalization.

Obviously, the same criteria for selection of patients, contraindications, conduct, and precautions employed for spinal anesthesia with other drugs are applicable to this technique.

REFERENCES

1. Lemmon, W. T.: A Method for Continuous Spinal Anesthesia, *Ann. Surg.* 111: 141-144, 1940.
2. Tuohy, E. B.: Continuous Spinal Anesthesia: Its Usefulness and Technique Involved, *Anesthesiology* 5: 142-148, 1944.
3. Sise, L. F.: Pontocaine-Glucose Solution for Spinal Anesthesia, *S. Clin. North America* 15: 1501-1511, 1935.
4. Jones, W. H.: Spinal Analgesia; A Method and a New Drug Percaine, *Brit. J. Anaesth.* 7: 99-113, 1930.
5. Wilson-Etherington, W.: Intra-thecal Nerve Rootlet Block: Some Contributions: A New Technique, *Anesth. & Analg.* 14: 102-110, 1935.
6. Silvertown, R. J.: Spinal Analgesia; the Percaine-Ephedrine Technique, *Australian & New Zealand J. Surg.* 3: 223-234, 1934.
7. Sankey, B. B., and Whitacre, R. J.: Nupercaine and Dextrose, 1:1500 Solution for Spinal Anesthesia, *Anesthesiology* 2: 203-205, 1941.
8. Adriani, J.: Unpublished experimental data.
9. Goodman, L., and Gilman, A.: *Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Company, p. 297.
10. Co Tui, Preiss, A. L., Barcham, I., and Nevin, Marshall I.: Local Nervous Tissue Changes Following Spinal Anesthesia in Experimental Animals, *J. Pharmacol. & Exper. Therap.* 81: 209, 1944.

PULMONARY COMPLICATIONS FOLLOWING APPENDECTOMY AND HERNIORRHAPHY

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THE pulmonary complications following 400 operations for hernia and 361 operations for appendicitis in the Station Hospital, Camp Rucker, Ala., are shown in this paper. An insignificant number of the cases of appendicitis were in women and all of the hernias were in men. This is a report of pulmonary complications following lower abdominal operations on healthy young men between 18 and 40 years of age, using spinal anesthesia (150 mg. novocain) as the routine anesthetic, from July, 1942, until May 15, 1944.

The differentiation of atelectasis, bronchitis, pneumonitis, and broncho-pneumonia is dependent upon clinical observation with roentgenographic studies. Spink and Bellis¹ have noted that it is not always possible to be sure of the exact pathology in the early and minimal cases. King² believes that the presence of a bronchitis is the cause of the secretion that accumulates in the bronchial tree and may result in atelectasis. King has shown that the incidence of pulmonary complications varies with the interest taken in the subject, reporting 3.7, 5.2, and 6.8 per cent being present during successive years. Haight and Ransom³ state that atelectasis is most common after upper abdominal surgery, that it is twice as frequent in men as in women, that it is twice as frequent after gastric surgery as it is following biliary surgery, and that it occurs more frequently in individuals with a chronic cough, chronic bronchitis, sinusitis, asthma, or an acute cold. Oswald⁴ found the incidence twice as high in those over 40 years of age, an incidence of 5 per cent after hernia and appendix operations, and an incidence of 20 to 30 per cent after upper abdominal surgery. Maier⁵ reports an incidence of 10 per cent of atelectasis in the pulmonary remnant after lobectomy for bronchiectasis without a fatality, but states that Gower reported 33 per cent atelectasis in 154 cases of lobectomy for bronchiectasis, and that one-third of the deaths were due to suppuration in the unexpanded portion of the lung.

Table I shows that there were 35 patients (4.6 per cent) with pulmonary complications, following 761 operations for hernial repair or some type of appendicitis.

There was an incidence of 5.5 per cent (or 22) pulmonary complications after 460 herniorrhaphies. Thirteen (or 3.6 per cent) pulmonary

TABLE I

TYPE OF OPERATION	NUMBER OF OPERATIONS	NUMBER OF PULMONARY COMPLICATIONS	PER CENT
<i>Total operations for hernia or appendicitis</i>	761	35	4.6
<i>Total hernia operations</i>	400	22	5.5
Bilateral inguinal hernia	101	12	11.9
Right inguinal hernia	166	3	1.8
Left inguinal hernia	95	7	7.4
<i>Total operations for appendix pathology</i>	361	13	3.6
Operations for gangrenous appendix	28		
Perforated appendix	14		
Appendical abscess	7		
	49	5	10.4
Operations for simple appendicitis	312	8	2.6

complications followed 361 operations for appendicitis. There was an incidence of 11.9 per cent following 101 bilateral hernias, an incidence of 1.8 per cent following 166 right inguinal herniorrhaphies, and an incidence of 7.4 per cent following 95 left inguinal herniorrhaphies. The incidence was 10.4 per cent after 49 operations for gangrenous or perforated appendicitis or appendical abscess.

Table II shows that atelectasis alone was present in 12 cases and atelectasis with pneumonitis was present in 5 cases. Bronchopneumonia was present 4 times, bronchitis 13 times, and a lobular infarct occurred in the left base in 1 case. Lobar atelectasis was present in 10 cases, one-half of these being in the left lower lobe. Massive atelectasis occurred once in the right lung and once in the left lung.

TABLE II
TYPES OF COMPLICATIONS

Atelectasis alone		12 (Right lung, 5; left lung, 7)
Upper lobe	3	
Right	2	
Left	1	
Lower lobe	7	
Right	2	
Left	5	
Massive	2	
Right	1	
Left	1	
Atelectasis with pneumonitis		5
Bronchopneumonia		4
Bronchitis		13
Lobular infarct left base		1

Table III shows that atelectasis was present in 12 of the 22 patients with complications following hernia operations and was present 5 times in 13 patients with complications following operations for appendicitis.

Spinal anesthesia was used routinely and there were 32 (or 4.8 per cent) complications after 671 spinal anesthetics. There were two (or 3.9 per cent) complications following 51 spinal anesthetics supplemented with general anesthesia. It is generally felt that the anesthetic is not a

TABLE III

Complications following hernia operations	
Atelectasis alone or with pneumonitis	12
Bronchopneumonia or bronchitis	10
Total	22
Complications following appendicitis operations	
Atelectasis alone or with pneumonitis	5
Bronchopneumonia or bronchitis	7
Lobular infarct	1
Total	13

great factor in causing pulmonary complications or that spinal anesthesia will prevent pulmonary complications.

There was no mortality in the 761 cases. Delay in aeration of an atelectatic lobe occurred in two cases. In one case the first film was made twenty-four hours postoperatively (Aug. 27, 1943) and showed a beginning atelectasis. Under routine treatment including sulfadiazine there were no symptoms or fever that could not be explained by the abdominal condition. However, an x-ray view taken Sept. 6, ten days postoperatively, shows a well-developed right, upper lobar atelectasis. This was not producing any symptoms or fever. An x-ray taken September 13 showed a marked clearing of the process and the lung was entirely clear September 27. There were no patients with lobar pneumonia. A small infarct occurred in one case in the left base, obliterating the costophrenic angle and causing a density on the radiograph that was reported present one month after discharge from the hospital, but not producing any symptoms.

Prevention of pulmonary complications is possible by attention to many details that influence and predispose to its occurrence. In one-third of our cases there was a history of respiratory infection, tooth infection, or sinusitis immediately prior to, or at the time of, operation. The eradication of infection in the nose, mouth, or respiratory tract and lapse of period of 7 to 14 days before operation is desirable. An acute phase of a chronic pulmonary infection in the presence of bronchiectasis should be allowed to subside completely. The pulmonary bronchial system before, during, and after the operation should be kept clear. For these lower abdominal cases the patient was asked to clear his bronchi prior to operation and a slight Trendelenburg position was used during the operation. The patients were usually ventilated at the end of operation with carbon dioxide and the importance of deep breathing, coughing, expectorating, and moving the legs was stressed. They were encouraged to cough, and were assisted in coughing. When bronchial secretion was obviously present and the patient was having difficulty expectorating, carbon dioxide oxygen ventilation was given twice daily. Sulfadiazine, 1 Gm., with sodium bicarbonate, 1 dr., was given six times daily with a fluid intake sufficient to give a urinary output of 1,000 c.c. or more.

Very little has been written about the psychologic inhibition of coughing that has played a part in the development of atelectasis in many of our cases, especially in the cases of massive atelectasis encountered at the onset of the series. Coughing causes a pain in the wound and the soldier thinks of tearing the repair with the development of another hernia, which is a real, tangible, experience, whereas he probably has never heard of pulmonary complications. In the great majority of cases this is easily overcome by explanation before operation, repeated during the operation by the anesthetist, and by frequent visits, reassurance, and personal contact postoperatively. Not the least of this reassurance is aiding the patient in coughing by holding his wound while he coughs and at times giving a few sharp slaps on the back. To reinforce this psychotherapy and actually stimulate deep breathing, carbon dioxide and oxygen inhalations have been used frequently for a few days. This is of more value after herniorrhaphy since two weeks flat in bed, or more, are necessary postoperatively, whereas with the simple appendectomies with a McBurney incision the patient is given freedom to do as much as he will and encouraged to early sitting and walking.

The treatment of atelectasis and bronchitis is usually satisfactory with the use of inhalations, sulfadiazine, and more energetic working with the patient for him to cough up the secretions. Frequent radiographic studies, at least daily for a few days, are necessary to establish the aeration status of the lungs. If conservative measures are not successful, aspiration of the plugs and establishment of a clear airway are necessary. Haight and Ransom recommend the use of a soft No. 16 French urethral catheter when frequent aspirations are needed, and the patient is not cyanotic. Bronchoscopic aspiration is necessary if these measures are not successful.

SUMMARY

There were 35 (or 4.6 per cent) pulmonary complications following 761 operations for hernias and for pathologic conditions resulting from disease of the appendix in a station hospital during the past two years. There was no mortality following these operations.

Pulmonary complications were present in 10.4 per cent of 49 operations for severe appendicitis and 2.6 per cent of 312 operations for uncomplicated appendicitis.

There were 22 (or 5.5 per cent) pulmonary complications after 400 operations for hernia.

Atelectasis was present alone or in combination in 17 cases and bronchitis or bronchopneumonia was present in 17 cases. There was one small pulmonary infarct.

We do not believe that the use of spinal anesthesia is a factor in the development of postoperative pulmonary complications.

The presence of infection of the upper respiratory tract, sinuses, teeth, tonsils, or the lungs will increase the development of pulmonary complications.

Prevention of atelectasis is best accomplished by the preservation and activation of the normal cough by reassurance, adequate explanation of the objective to the patient, and the employment of turning, deep breathing, slapping on the back, and CO₂ inhalations as adjuvants of psychotherapy all combining to result in normal expectoration by the patient of the bronchial secretions.

Sulfadiazine and sodium bicarbonate are used routinely with pulmonary complications because of the frequent impossibility of differentiating infection from atelectasis early in the process and because atelectasis is frequently associated with infection.

Catheter aspiration or bronchoscopy is advocated if conservative measures fail.

REFERENCES

1. Spink, Wesley W., and Bellis, Carroll: Sulfathiazole and Sodium Sulfathiazole in the treatment of Postoperative Pneumonia, *Surg. Gynec. & Obst.* 72: 989, 1941.
2. King, D. S.: Postoperative Pulmonary Complications: II. CO₂ as a Preventive in a Controlled Series, *J. A. M. A.* 100: 21, 1933; Postoperative Pulmonary Complications, *Surg., Gynec. & Obst.* 56: 43, 1933.
3. Haight, Cameron, and Ransom, Henry K.: Observations on the Prevention and Treatment of Postoperative Atelectasis and Bronchopneumonia, *Ann. Surg.* 114: 243, 1941.
4. Oswald, N. C.: Some Aspects of Postoperative Pulmonary Complications, *Proc. Royal Soc. Med.* 31: 1272, 1938.
5. Maier, Herbert C.: Surgical Treatment of Bronchiectasis, *SURGERY* 15: 789-800, 1944.

CARDIOVASCULAR DISTURBANCES FOLLOWING PNEUMONECTOMY

AN ATTEMPT TO CORRELATE BLOOD PRESSURE AND INTRAPLEURAL PRESSURE CHANGES

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CARDIOVASCULAR disturbances during and immediately after pneumonectomy have been noted by many observers and have been the object of considerable attention. The problem is no less complex than the whole subject of cardiovascular physiology. Many factors have been suggested as being responsible for these changes; many factors, undoubtedly, operate.

In our experience a considerable decrease of blood pressure is commonly noted immediately after removal of a patient from the operating table to the bed in his room. Maier¹ suggested that after pneumonectomy, changes in intrapleural pressure incident to change in the position of the body of the patient may be responsible for sudden drops in blood pressure and changes in the character of the pulse. In order to test this hypothesis and in an attempt to throw more light on this problem, we have measured, in five cases, intrapleural pressure in three positions immediately after closure of the thoracic wall following pneumonectomy, and have taken simultaneous records of the blood pressure and the pulse rate.

FREQUENCY, MAGNITUDE, AND DURATION OF THE FALL OF THE BLOOD PRESSURE OF PATIENTS IMMEDIATELY AFTER PNEUMONECTOMY

The records of twenty-eight patients on whom pneumonectomy had been performed were studied to determine the frequency and magnitude of a significant fall of blood pressure on the return of the patient from the operating room to his hospital room. Of these twenty-eight, seventeen (61 per cent) had a significant drop (average 35 mm. of mercury).

The duration of the abnormal reduction of blood pressure varied widely, with forty minutes the minimum and forty-eight hours the maximum. The average time required for return of the pressure to approximately normal (that is, preoperative) levels was 9.6 hours.

In order to establish some basis for comparison, nine cases in which transthoracic exploration for inoperable carcinoma of the cardia of the stomach or of the lower end of the esophagus had been performed and nine cases in which partial gastrectomy for carcinoma or for duodenal ulcer had been performed were used to determine the frequency and magnitude of decreases of blood pressure in the same immediate post-operative period.

Received for publication, Dec. 13, 1944.

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In the group of cases in which transthoracic exploration was performed, six patients had no appreciable change in blood pressure during this period. Three had transitory falls to 70 to 90 mm. of mercury systolic, but their blood pressure rose to normal in the next one to three hours.

In the second group of nine cases in which partial gastrectomy was performed, only one patient had an appreciable fall in pressure. This was a man aged 64 years, whose pressure fell from 144/80 to 110/64, but steadily and rapidly rose to its preoperative level. There was little in his history to suggest heart disease but he died of coronary occlusion on the fourth postoperative day.

To summarize, in only four of eighteen cases in which rather extensive surgical procedures had involved the thoracic and abdominal cavities was there an appreciable fall of blood pressure between the departure of the patient from the operating room and his arrival in the hospital room. In no case was the fall great nor was it of long duration. This result is in rather striking contrast to the group in which pneumonectomy was performed.

DESCRIPTION OF METHOD

Intrapleural pressures were measured by means of a U manometer (water) immediately on closure of the thoracic wound in five cases in which pneumonectomy had been performed.

In four instances pressures were measured through a 24 F. rubber catheter, which had been allowed to remain in the wound during closure. Gentle suction through the catheter was applied throughout the procedure of closure in order to prevent the development of tension pneumothorax by the valve action of the intercostal structures from the time they were loosely brought together preparatory to suture until the thoracic wall was closed in an airtight manner by suture. In each case the thorax was closed securely before pressure readings were taken and the first intrapleural pressure was nearly the same as atmospheric pressure.*

With the patient successively in the lateral horizontal position, in the dorsal horizontal position, and in the dorsal position with the head of the table elevated 30 degrees, intrapleural pressures were measured. The patient had remained in the lateral position with the pneumonectomized side up throughout the course of the operation and the first measurement was made before this position was altered. Simultaneously, the blood pressure and pulse rate were determined.

Intervals between measurements in the three positions varied from one to three minutes, or the time, in each instance, consumed in changing the patient's position and in making the necessary measurements.

*There was one exception, in Case 2, in which because of failure to regulate suction considerable negative pressure developed.

PREOPERATIVE MEDICATION

In each case preoperative medication had been the same: $1\frac{1}{2}$ gr. (0.1 Gm.) of soluble pentobarbital (nembutal) on the evening before operation, $1\frac{1}{2}$ gr. (0.1 Gm.) of soluble pentobarbital at 7 A.M. on the day of operation, and $\frac{1}{6}$ gr. (0.01 Gm.) of morphine sulfate and $\frac{1}{150}$ gr. (0.00043 Gm.) of atropine sulfate approximately one hour before the induction of anesthesia.

ANESTHETIC AGENTS EMPLOYED

In every case anesthesia was induced with nitrous oxide and oxygen, to which mixture ether was added subsequently. The mixture was administered with a closed system through an intratracheal tube.

INTRAPLEURAL PRESSURE RECORDS

Depending on the surgical findings regarding the state of the pleura and the consequent mobility of the mediastinum, the cases could be divided into two groups: (1) those with thickened pleura and an immobile (fixed) mediastinum (two cases); and (2) those with thin pleura and a mobile mediastinum (three cases).

In those of the first group, there were no significant changes (that is, changes that could be measured accurately with this method) in intrapleural pressure with changes in position.

In the second group, in which the mediastinal pleura had appeared grossly normal and in which the mediastinal mobility had been apparent with respiratory motion while the thorax was open, there was a considerable rise in intrapleural pressure with the change from a lateral horizontal to a dorsal horizontal position and a lesser but measurable change to a lower pressure with elevation of the head of the table 30 degrees.

The position of the mediastinum as shown by the roentgenogram of the thorax made immediately after operation was considered as reflecting the pressure differential between the two sides of the thorax (if the mediastinum was not rendered immobile by pleural thickening). In the absence of atelectasis in the remaining lung, shift of the mediastinum away from the side of the pneumothorax invariably meant an abnormally high intrapleural pressure on that side. Thus, in a number of cases in which measurements of intrapleural pressure had not been made, abnormal position of the mediastinum in an early postoperative roentgenogram of the thorax gave indirect evidence of significant deviation of intrapleural pressure from the normal and so afforded observations pertinent to this study.

CORRELATION OF INTRAPLEURAL PRESSURE, BLOOD PRESSURE, AND PULSE RATE

In those cases (Cases 1 and 2) in which the pleura was thickened and the mediastinum was thus rendered immobile, our measurements failed to show any significant change in intrapleural pressure with changes in

position. Yet in each instance there were minor drops in blood pressure during these maneuvers and a considerable fall in blood pressure between the time when it was last recorded immediately before departure from the operating room and the time when it was first recorded on arrival in the patient's room ten to twenty minutes later. In both cases there was a slight increase in the pulse rate with the fall in blood pressure. Within a few hours after return to the hospital room, the blood pressure gradually rose to normal preoperative levels and the general condition of the patient was never considered to be alarming. Intrapleural pressure had been adjusted to approximately atmospheric levels and the mediastinum was shown by roentgenogram to be in the midline when the patient was lying on his back.

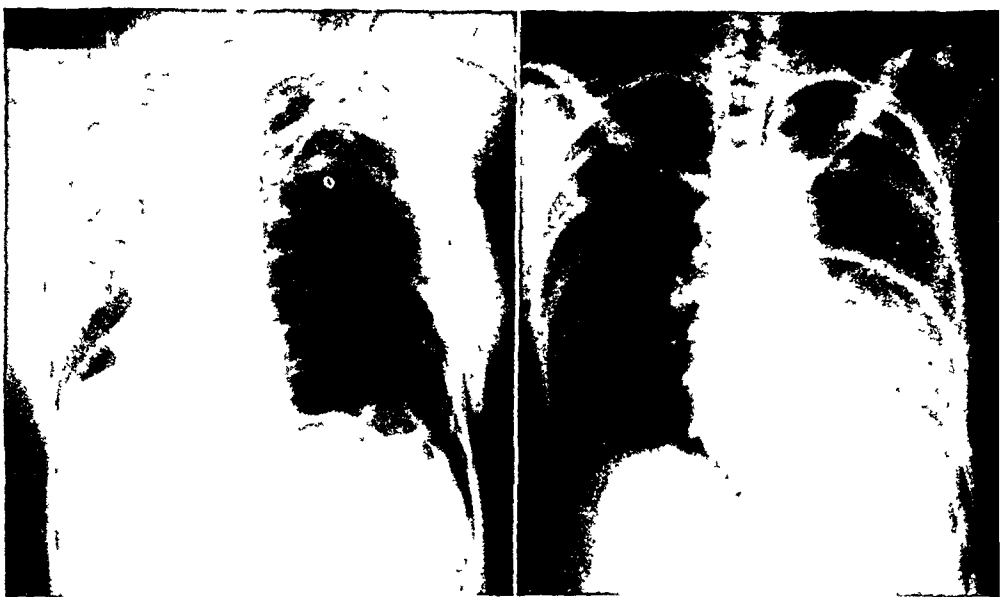
In Cases 3, 4, and 5, in which the pleura appeared normal and the mediastinum mobile, there were changes in the intrapleural pressure with changes in the position of the patient. These changes were of similar magnitude in each of the three cases. In Case 3 there was no measurable change in blood pressure or pulse rate during these maneuvers. In Case 4 there was a fall in systolic pressure of 5 mm. of mercury and in diastolic pressure of 10 mm. without significant change in the pulse rate. These changes of blood pressure disappeared within a few minutes, before the patient could be removed from the table. In Case 5 the reaction was similar to that in Case 4 except for a slight slowing of the pulse during the period of pressure measurements.

In each of these three cases there had been a considerable rise of intrapleural pressure in the empty pleural cavity with change from a lateral to a dorsal position, but in no case was there any considerable difference between the blood pressures or the pulse rates as recorded in the two positions. Postoperative roentgenograms of the thorax with the patient in the dorsal horizontal position showed the mediastinum in the midline.

Observations on the blood pressure and pulse rate during the same period were made in three other cases (Cases 6, 7, and 8) in which intrapleural pressure measurements were not made but in which immediate postoperative thoracic roentgenograms gave indirect evidence on intrapleural pressure. It has been suggested that changes of intrapleural pressure are important chiefly because of their effect on the position of the mediastinum. In Case 6 there was a drop from 105/70 to 85/60 when the patient was turned on her back and held in a head-and-shoulders-up position (propped up approximately 30 degrees) while a dressing was being applied. Thirteen minutes later the pressure had returned to 110/75 while she was lying on her back. Immediate postoperative roentgenograms in this position showed the mediastinum in the midline. Elevation of the head rather than the change from the lateral to the dorsal position seemed to be responsible for the transitory fall of blood pressure. In Case 8 there was no change of blood pressure during this maneuver, although there was

some fall subsequently during bronchoscopic aspiration. In this case a thoracic roentgenogram showed a slight shift of the mediastinum to the good side but of such minor degree that no adjustment of the intrapleural pressure was deemed necessary.

Case 7 is particularly interesting and pertinent to this study. Suction was not applied to the pleural space during closure and an abnormally high intrapleural pressure was inadvertently allowed to develop with a resulting considerable shift of the mediastinum away from the



A.

B.

Fig. 1 (Case 7) —A. The thorax immediately after pneumonectomy. The considerable shift of the mediastinum to the right is apparent. B. A few hours later, after the withdrawal of air from the side of the pneumothorax and the adjustment of intrapleural pressure to approximately atmospheric level (see Fig. 2). Both views were made with the patient lying flat on her back.

side of the pneumothorax. This was discovered in the routine thoracic roentgenogram taken on arrival of the patient in her room. Two hundred cubic centimeters of air were withdrawn without visible change in the position of the mediastinum or change in the blood pressure or pulse rate. With the pneumothorax apparatus an additional large volume (approximately 700 c.c.) of air was withdrawn and the pressure adjusted to approximately atmospheric level. This required about five minutes. There was no change in the blood pressure or pulse rate, although the respiratory rate fell almost immediately from 24 per minute to 16 per minute. A roentgenogram of the thorax taken a few minutes later showed the mediastinum to have returned to its normal midline position (Figs. 1 and 2).

Of the eight patients just considered, two had mediastinal shift: one without a fall in blood pressure; the other with a slight fall in

blood pressure, which was unaffected by relief of the tension pneumothorax and the return of the mediastinum to the midline. Of the six patients without mediastinal shift, three had known changes in intrapleural pressure associated with change in position of the body but without demonstrable effect on the blood pressure or pulse rate. Though there was no apparent correlation of the blood pressure and pulse rates with changes in intrapleural pressure, a fall of blood pressure was demonstrated in six of the eight cases during the period of return of the patient from the operating room.

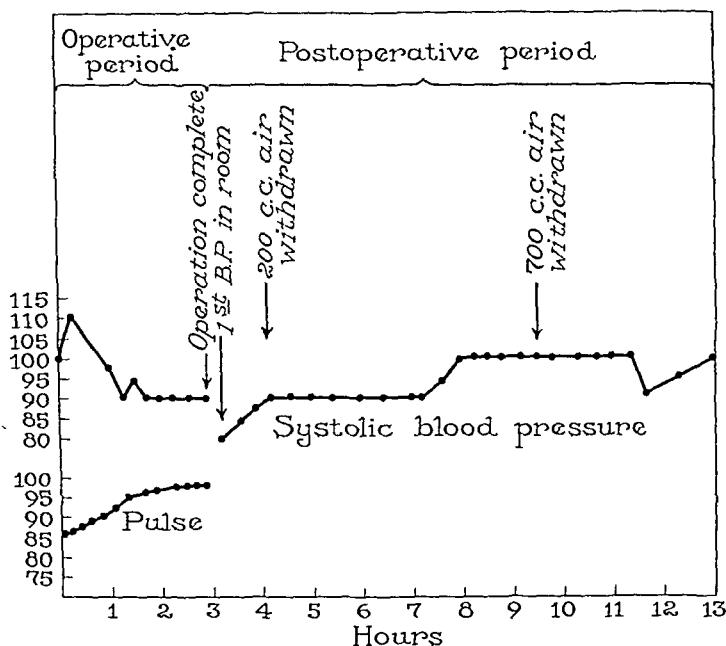


Fig. 2.—Systolic blood pressure during the operative and early postoperative period in Case 7. Time at which tension pneumothorax was relieved by the withdrawal of 700 c.c. of air is indicated. The failure of relief of pneumothorax to influence systolic blood pressure is apparent. Although the pulse rate for the postoperative period is not shown here, it too was unchanged.

It has already been pointed out that in a series of twenty-eight cases of pneumonectomy done prior to this study, there was a considerable postoperative fall of blood pressure in 61 per cent, so that the proportion in the combined series is 64 per cent. A further analysis of the series of twenty-eight cases on the basis of the presence or absence of mediastinal shift is of some interest. Roentgenograms of the thorax made immediately after operation showed the mediastinum in the midline in sixteen and with a slight shift (always to the good side) in twelve. In nine of the group of sixteen cases in which the mediastinum was in the midline, a fall of blood pressure occurred in the immediate postoperative period. The average fall was 32 mm. of mercury systolic and the period required for return to normal varied from two to thirty hours (Table I).

TABLE I

DATA ON TWENTY-EIGHT CASES IN WHICH PNEUMONECTOMY WAS PERFORMED

CHARACTERISTIC	POSITION OF MEDIASTINUM AS SHOWN BY IMMEDIATE POSTOPERATIVE ROENTGENOGRAM			
	MEDIASTIUM IN MIDLINE		MEDIASTINAL SHIFT	
	NO POSTOPERA-TIVE FALL OF BLOOD PRESSURE	POSTOPERA-TIVE FALL OF BLOOD PRESSURE*	NO POSTOPERA-TIVE FALL OF BLOOD PRESSURE	POSTOPERA-TIVE FALL OF BLOOD PRESSURE†
Total patients	7	9	4	8
Male	6	8	3	7
Female	1	1	1	1
Side of pneumonectomy				
Right	5	6	1	3
Left	2	3	3	5
Age of patient (years)				
10 to 19		1	1	
20 to 29	2			
30 to 39			1	1
40 to 49		6		1
50 to 59	3	1	2	4
60 to 69	2	1		2

*Average fall 32 mm. of mercury systolic. Blood pressure returned to normal levels in two to thirty hours.

†Average fall 44 mm. of mercury systolic. Blood pressure returned to normal levels in forty minutes to forty-eight hours.

In twelve cases there were minor degrees of shift of the mediastinum. In eight of this group there were immediate postoperative decreases of blood pressure averaging 44 mm. of mercury systolic and requiring forty minutes to forty-eight hours for return to normal preoperative range. In four cases in which there was mediastinal shift there was no significant change of blood pressure (Table I).

The side on which pneumonectomy was performed seemed to have no influence on this phenomenon; age was apparently not a factor of importance (Table I).

FACTORS INFLUENCING BLOOD PRESSURE AND PULSE RATE DURING AND IMMEDIATELY AFTER PNEUMONECTOMY

Loss of blood may be considered briefly as a possible factor in this phenomenon of fall of blood pressure. Considerable loss of blood is, in many of these cases, inevitable but an attempt was made in each case to compensate for loss of blood by transfusion of whole citrated blood during the operative procedure. The amount of blood given was determined by an estimation of the amount of blood lost and by the stability of the blood pressure and pulse rate during the operation. There was usually little change in the concentrations of hemoglobin estimated preoperatively and in the early (after forty-eight hours) postoperative period, indicating that replacement had about equaled blood lost. In no case of this entire group (thirty-six) was there postoperative evidence of gross hemorrhage into the empty pleural space. When it seemed advisable to remove fluid which had accumulated in the pleural space some days after pneumonectomy, this fluid was uni-

formly found to be grossly bloody but it was thin and lacked the appearance of whole blood. It was considered in each case to be a bloody effusion.

Observations on three patients suggested that lack of oxygen may have played a role in the temporary fall of blood pressure. The patient in Case 2 arrived in his room at 2:25 P.M., when his blood pressure was 85 mm. of mercury systolic and 52 diastolic. At 2:45 it was still 88 mm. of mercury systolic and 50 diastolic. In five more minutes he was placed in an oxygen tent and twenty-five minutes later the pressure had risen to 104 mm. of mercury systolic and 60 diastolic. In Case 6 the systolic pressure remained about 100 mm. of mercury during the first twenty-four hours. At the end of this time the patient was taken out of the oxygen tent for one hour, during which she became quite pale, her nail beds became slightly cyanotic, and her blood pressure promptly fell from 100/60 to 66/40. After her return to the oxygen tent, the pressure rapidly rose to the previous level. Change in her position in bed seemed to have no effect on her blood pressure. At the completion of the operation in Case 8 the blood pressure was 115 mm. of mercury systolic and 70 diastolic, the pulse rate 132 per minute, and the pulse was regular. Immediately after bronchoscopic aspiration, the pressure was found to have fallen to 95 mm. of mercury systolic and 60 diastolic, and the pulse had become more rapid and somewhat irregular. The patient's condition rapidly improved with the administration of oxygen by mask.

There is another consideration of some interest in this connection. During the final steps in the closure of the thoracic wall, the administration of the anesthetic agent is usually discontinued but the administration of oxygen by mask is continued until bronchoscopic aspiration is carried out. Immediately after this procedure, oxygen is again given for a few minutes until the patient's color has returned to normal. The period of his transportation from the operating room to the hospital room and until the first determination of blood pressure is made is usually of fifteen to twenty minutes' duration. During this period no oxygen was administered: otherwise the conditions under which the patient existed were no different from those during the final twenty to thirty minutes spent on the operating room table. Perhaps the return toward consciousness with recovery from the anesthetic lessens neural thresholds generally and permits the initiation of cardiovascular reflexes which are responsible for these changes of the blood pressure and pulse rate. These reflexes will be considered later. There are at least two considerations opposed to this argument: one is that the patient is still in a rather deep plane of anesthesia and usually does not begin to respond to external stimuli for another hour or more; the other is that in the experimental animal cardiovascular reflexes have been shown to exist during deep surgical anesthesia.

There are so many factors which directly or indirectly influence the blood pressure and the pulse rate that these observations suggesting a possible role for anoxia must be offered with caution. However, it is known that in man anoxia can cause a lowering of the blood pressure,² an increase in the rate and frequency, and an irregularity in the rhythm of the heart beat.³ Maier and Cournand⁴ found a reduction in the arterial oxygen saturation following pneumonectomy. This reduction lasted for several days. None of their determinations of arterial oxygen saturation were made, however, in the early postoperative period while the influence of the anesthetic agent remained. We have no direct data on the oxygen content of arterial blood during that period but our observations, together with the experimental work just cited, support the possibility that anoxia may be present in a significant degree at this period and that it may play a causative role in the lowering of the blood pressure.

The part played by cardiovascular reflexes initiated at the pulmonary stump and mediated through the vagus nerve during the recovery from anesthesia has previously been alluded to. Reflex disturbances initiated by operative manipulation and by direct electrical stimulation of the structures in the root of the lung have been experimentally investigated most recently by O'Shaughnessy.⁵ He found that blocking the vagus was not a safeguard against such reflex disturbances. Respiratory reflexes were thereby abolished but cardiovascular reflexes remained. No immediate changes in pulse, blood pressure, or respiration have been noted on application of clamps to structures in the root of the lung in this present series of cases in which pneumonectomy has been performed. Arce and Brea⁶ stated that vascular reflexes of this origin "may be manifested by sudden drop in blood pressure, bradycardia, extrasystoles, auriculoventricular dissociation, and ventricular fibrillation. . . . The intensity, degree, and severity of these phenomena vary considerably and cannot be foreseen."

As has been previously noted, these same cardiovascular effects can be produced by serious degrees of anoxia. The true role of either anoxia or vagal reflexes in the production of cardiovascular disturbances associated with pulmonary resection has not yet been established. Certainly, as suggested by O'Shaughnessy, unrecognized and unrecognizable reduction of cardiac reserve in some of these cases must exist preoperatively and be a factor in this phenomenon. It seems safe to say that slight to moderately abnormal intrapleural pressure in the side of the pneumothorax with mediastinal shift does not play an important part.

SUMMARY

Rather severe fall of blood pressure immediately following pneumonectomy has been noted commonly. In 64 per cent of a series of thirty-six cases herein reported such a drop occurred. Abrupt changes of the intrapleural pressure on the side of the pneumothorax, which were

produced by changes in the position of the body of the patient, were investigated as a possible cause.

Determinations of intrapleural pressure were made on five patients immediately after closure of the thorax after pneumonectomy. These determinations were made with the patient in three positions. Simultaneous records of the blood pressure and pulse rate were kept. Records of a number of other patients were reviewed for data pertinent to this study.

In cases in which the mediastinum was mobile, changes in the position of the patient produced changes in the intrapleural pressure, but no constant change in the blood pressure or pulse rate could be correlated with this change.

As factors in this postoperative lowering of the blood pressure, hemorrhage, anoxia, and cardiovascular reflexes mediated through the vagus were briefly considered.

REPORT OF CASES

CASE 1.—The patient was a man, aged 42 years. On April 6, 1944, left pneumonectomy was performed for saccular bronchiectasis secondary to multiple pulmonary abscesses. The pleural cavity was completely obliterated but adhesions were not dense. The pleura, including the mediastinal pleura, was definitely ($\frac{1}{2}$ inch [0.3 cm.]) thickened. The mediastinum appeared immobile.

Immediately after closure of the wound the intrapleural pressure was determined by means of a 15 gauge needle inserted in the fifth interspace in the mid-axillary line. At 1 P.M., while the patient was lying on his right side, the blood pressure was 110 mm. of mercury systolic and 65 diastolic; the pulse rate was 100 per minute. The intrapleural pressure was -4 cm. of water on inspiration and +8 cm. on expiration. At 1:02, while the patient was lying on his back in a horizontal position, the blood pressure was 100 mm. of mercury systolic and 60 diastolic; the pulse rate was 100 per minute. The intrapleural pressure was -4 cm. of water on inspiration and +8 cm. on expiration. At 1:05, while the patient was lying on his back, with his head and shoulders elevated approximately 30 degrees, the blood pressure was 100 mm. of mercury systolic and 60 diastolic, and the pulse rate was 104 per minute. The intrapleural pressure was -2 cm. of water on inspiration and +6 cm. on expiration.

At 1:20 P.M. the first determination of blood pressure made after the patient's return to his room showed a systolic pressure of 80 mm. of mercury and a diastolic pressure of 40. The pulse rate was 110. In four hours the blood pressure rose to 110/60 and the pulse rate fell to 90 per minute. Both remained stable thereafter.

A roentgenogram of the thorax made two hours after operation showed no mediastinal shift.

One thousand cubic centimeters of whole citrated blood were given during the operation. The concentration of hemoglobin was 12.7 Gm. per 100 c.c. of blood before the operation and 13.7 Gm. forty-eight hours after the operation.

CASE 2.—The patient was a man, aged 50 years. On April 13, 1944, left pneumonectomy was performed for bronchogenic carcinoma. There were dense pleural adhesions surrounding the upper lobe on all sides and thin fibrous adhesions over the entire surface of the lung. The mediastinum had little mobility.

Suction was applied by catheter (without proper regulation) while the thoracic wall was being closed. When the initial attempt to measure intrapleural pressure was made, the negative pressure was so great that the fluid in the manometer was

There are so many factors which directly or indirectly influence the blood pressure and the pulse rate that these observations suggesting a possible role for anoxia must be offered with caution. However, it is known that in man anoxia can cause a lowering of the blood pressure,² an increase in the rate and frequency, and an irregularity in the rhythm of the heart beat.³ Maier and Cournand⁴ found a reduction in the arterial oxygen saturation following pneumonectomy. This reduction lasted for several days. None of their determinations of arterial oxygen saturation were made, however, in the early postoperative period while the influence of the anesthetic agent remained. We have no direct data on the oxygen content of arterial blood during that period but our observations, together with the experimental work just cited, support the possibility that anoxia may be present in a significant degree at this period and that it may play a causative role in the lowering of the blood pressure.

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As has been previously noted, these same cardiovascular effects can be produced by serious degrees of anoxia. The true role of either anoxia or vagal reflexes in the production of cardiovascular disturbances associated with pulmonary resection has not yet been established. Certainly, as suggested by O'Shaughnessy, unrecognized and unrecognizable reduction of cardiac reserve in some of these cases must exist preoperatively and be a factor in this phenomenon. It seems safe to say that slight to moderately abnormal intrapleural pressure in the side of the pneumothorax with mediastinal shift does not play an important part.

SUMMARY

Rather severe fall of blood pressure immediately following pneumonectomy has been noted commonly. In 64 per cent of a series of thirty-six cases herein reported such a drop occurred. Abrupt changes of the intrapleural pressure on the side of the pneumothorax, which were

CASE 4.—The patient was a man, aged 48 years. On May 22, 1944, right pneumonectomy was performed for bronchogenic carcinoma. There was no pleural thickening. The pleural sac was free of adhesions; the mediastinum was mobile.

Measurements of intrapleural pressure were taken through a catheter, which had been used for maintenance of gentle suction during closure. At 2:28 P.M., while the patient was lying on his left side, the blood pressure was 100 mm. of mercury systolic and 60 diastolic. The pulse rate was 84 per minute. The intrapleural pressure was -12 cm. of water at the interrespiratory phase, immediately before the onset of inspiration. At 2:31, while the patient was lying on his back in a horizontal position, the blood pressure was 105 mm. of mercury systolic and 70 diastolic; the pulse rate was 84 per minute. The intrapleural pressure at the interrespiratory phase was +2 cm. of water. At 2:32, while the patient was on his back with his head and shoulders elevated approximately 30 degrees, the blood pressure was 105 mm. of mercury systolic and 70 diastolic; the pulse rate was 96 per minute. The intrathoracic pressure at the interrespiratory phase was -2 cm. of water. At 2:37, while the patient was on his back in a horizontal position, the blood pressure was 110 mm. of mercury systolic and 80 diastolic; the pulse rate was 96 per minute.

CASE 5.—The patient was a man, aged 61 years. On June 8, 1944, right pneumonectomy was performed for bronchogenic carcinoma. There were no pleural adhesions. The mediastinum was mobile.

Measurements of intrapleural pressure were taken through a catheter, which had been used for maintenance of gentle suction during closure. Throughout the operative procedure the systolic blood pressure varied from 120 to 90 mm. of mercury. At the completion of the procedure it was 110 mm. The pulse rate, which was initially 80, rose to 100 per minute. At 2:11 P.M., after the incision had been closed and while the patient was lying on his left side, the blood pressure was 120 mm. of mercury systolic and 70 diastolic; the pulse rate was 84 per minute.

At 2:15 P.M., while the patient was lying on his left side, the blood pressure and pulse rate were the same as at 2:11. The intrapleural pressure at the interrespiratory phase, immediately before onset of inspiration, was +4 cm. of water. At 2:19, while the patient was lying on his back in a horizontal position, the blood pressure was 110 mm. of mercury systolic and 60 diastolic; the pulse rate was 76 per minute. His intrapleural pressure at the interrespiratory phase was +12 cm. of water. At 2:20, while the patient was on his back with his head and shoulders elevated approximately 30 degrees, the blood pressure was 105 mm. of mercury systolic and 60 diastolic; the pulse rate was 76 per minute. The intrapleural pressure at the interrespiratory phase was +6 cm. of water. At 2:30, immediately after bronchoscopic aspiration, the patient's blood pressure was 110 mm. of mercury systolic and 60 diastolic; the pulse rate was 88 per minute. He was given 100 per cent oxygen by mask. At 2:40, immediately before the patient left the operating room, the blood pressure was the same as at 2:30.

At 3 P.M. the first determination of blood pressure after the patient had been transported on a litter to his room and placed in bed was made while he was in a horizontal dorsal position. The blood pressure was 80 mm. of mercury systolic and 60 diastolic. Almost immediately he was placed in an oxygen tent. Within one hour the blood pressure had risen to 120 mm. of mercury systolic and 80 diastolic. During this period the pulse rate varied from 60 to 80 per minute. A roentgenogram of the thorax showed the mediastinum in the midline. Twelve hundred cubic centimeters of whole citrated blood were given during the operation.

The concentration of hemoglobin was 14.0 Gm. per 100 c.c. of blood before the operation and 12.3 Gm. forty-eight hours after the operation.

CASE 6.—The patient was a woman, aged 52 years. On June 12, 1944, right pneumonectomy was performed for bronchogenic carcinoma. There were no pleural

adhesions. The mediastinum was mobile. During closure, negative pressure of 6 to 8 cm. of water was applied to the right pleural cavity through a rubber catheter, which was withdrawn immediately after closure.

There was a brief episode of brisk hemorrhage from a small rent in the wall of the pulmonary artery. The systolic blood pressure fell to 70 mm. of mercury at this time but rose rapidly to satisfactory levels when the bleeding was controlled. At 1:30 P.M., while the patient was lying on her left side at the completion of the operation, the blood pressure was 105 mm. of mercury systolic and 70 diastolic.

The patient's head and shoulders were elevated about 30 degrees during application of a dressing to the wound. At 1:35 P.M., immediately after this had been done and while the patient was lying horizontally on her back, the blood pressure was 85 mm. of mercury systolic and 60 diastolic. From 1:35 to 1:45 bronchoscopic aspiration was performed. At 1:45 the patient's blood pressure was 100 mm. of mercury systolic and 70 diastolic. From 1:45 to 1:48 she was given 100 per cent oxygen by mask. At 1:48 the blood pressure was 110 mm. of mercury systolic and 75 diastolic.

At 2 P.M. the first determination of blood pressure after the patient's arrival in her room was made. At this time the blood pressure was 90 mm. of mercury systolic and 50 diastolic; the pulse rate was 128 per minute. One hour after this the blood pressure had risen to 100 mm. of mercury systolic and 60 diastolic; the pulse rate had fallen to 104 per minute.

The patient's blood pressure and pulse rate remained stable during the next twenty-four hours. At the end of this time she was taken out of the oxygen tent* for one hour. During this interval she became quite pale, her nail beds became slightly cyanotic, and her blood pressure fell abruptly from 100/60 to 66/40. After her return to the oxygen tent the blood pressure rose to the previous level and her general condition improved promptly.

One thousand cubic centimeters of whole citrated blood were given during the operation. The concentration of hemoglobin was 12.3 Gm. per 100 c.c. of blood before operation and 12.1 Gm. forty-eight hours after operation.

CASE 7.—The patient was a woman, aged 31 years. On June 12, 1944, left pneumonectomy was performed for a large bronchial adenoma. Some pleural adhesions were present but the mediastinum was mobile.

The thorax was closed without suction by catheter in the pleural space during the procedure. A roentgenogram of the thorax taken immediately after the operation revealed a considerable shift of the heart and other mediastinal structures to the right. Two hundred cubic centimeters of air were removed from the left pleural cavity without visible change in the position of the mediastinum and without apparent influence on the blood pressure or pulse rate. Several hours later, with the aid of the pneumothorax apparatus, intrapleural pressure was found to be approximately +16 cm. of water immediately before the beginning of inspiration. After the withdrawal of about 700 c.c. of air the pressure was reduced to -2 or -4 cm. of water. Another roentgenogram of the thorax showed that the mediastinum had returned to the midline. This readjustment of intrapleural pressure occupied about five minutes. There was no change of blood pressure or pulse rate, though the respiratory rate immediately fell from 24 per minute to 16 per minute (Figs. 1 and 2).

CASE 8.—The patient was a boy, aged 16 years. Left pneumonectomy was performed for marked saccular and cystic bronchiectasis involving the entire lung. There were thin fibrous adhesions over the entire surface of the lung. The mediastinum appeared fairly mobile. During closure, suction through a temporary catheter was maintained.

*All patients routinely are placed in an oxygen tent when they are returned to their rooms after pneumonectomy.

The blood pressure had remained stable throughout the procedure (100 to 108 mm. of mercury systolic). The pulse rate had risen from 80 to 120 per minute. At 12:30 P.M., while the patient was lying on his right side at the completion of closure of the incision, the blood pressure was 115 mm. of mercury systolic and 70 diastolic; the pulse rate was 132 per minute. The patient's head and shoulders were elevated approximately 30 degrees during the application of a dressing. At 12:35, while he was horizontal on his back, the blood pressure and pulse rate were the same as at 12:30. From 12:35 to 12:47 bronchoscopic aspiration was performed. At 12:47 the patient's blood pressure was 95 mm. of mercury systolic and 60 diastolic; the pulse was rapid and irregular. He was given 100 per cent oxygen by mask. At 12:50 the blood pressure was 90 mm. of mercury systolic and 60 diastolic; the pulse rate was 126 per minute and the pulse was regular.

At 1 P.M. the first determination of blood pressure after the patient's arrival in his room was made. The systolic pressure was 50 mm. of mercury; the diastolic pressure could not be determined. The patient was placed in an oxygen tent within a few minutes. At 1:30 the blood pressure was 80 mm. of mercury systolic and 50 diastolic; the pulse was of good volume and his skin was warm and dry. At 9 P.M. the blood pressure was 90 mm. of mercury systolic and 55 diastolic. At 10 P.M. his blood pressure was 100 mm. of mercury systolic and 60 diastolic.

A roentgenogram of the thorax taken immediately after operation showed very slight shift of the mediastinum to the right. This was so slight that readjustment of the intrapleural pressure was thought unnecessary.

REFERENCES

1. Maier, H. C.: Cardiopulmonary Disturbances Associated With Mediastinal Displacement After Pneumonectomy, *SURGERY* 15: 432-439, 1944.
2. Schneider, E. C., and Hedblom, C. A.: Blood Pressure With Special Reference to High Altitudes, *Am. J. Physiol.* 23: 90-104, 1908.
3. Greene, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension; VI. The Cause of the Changes Observed in the Heart During Extreme Anoxemia, *Am. J. Physiol.* 60: 155-192, 1922.
4. Maier, H. C., and Cournand, Andre: Studies of the Arterial Oxygen Saturation in the Postoperative Period After Pulmonary Resection, *SURGERY* 13: 199-213, 1943.
5. O'Shaughnessy, T. J.: The Vagus and Its Relation to the Surgery of the Thorax, *J. Thoracic Surg.* 5: 386-392, 1936.
6. Aronson, M. M.: Preliminary Phrenic-Vagus Inhibition in Thoracic Surgery, *J. Thoracic Surg.* 12: 544-547, 1943.

TUBERCULOUS ABSCESS OF THE THYROID GLAND

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THERE is at the present time a considerable amount of literature on tuberculous infection of the thyroid gland, a condition, however, considered rare by numerous surgeons with extensive experience in thyroid surgery. Rokitsansky¹ stated that tuberculosis of the thyroid gland was nonexistent, while Virchow² assumed it to be extremely rare. With the advent of thyroid surgery, case reports of tuberculosis of the thyroid gland began to appear in the literature, the diagnosis having been made in the majority of cases on the basis of extensive microscopic examinations of surgically removed goiters. All cases reported prior to 1913 were reviewed by Pollag,³ who added cases of his own. In this country, Mosiman in 1917,⁴ gave an excellent review of the literature at that time predominately European, and reported nine cases studied up to 1917 at the Crile Clinic. Collier and Huggins, in 1926,⁵ added five more cases to a list of 105 apparently proved cases of tuberculosis of the thyroid gland. Twenty-one cases were reported from the Mayo Clinic in 1932 by Rankin and Graham,⁶ together with 104 cases of surgically treated cases taken from the literature up to that time. Since then, case reports have been given by a number of clinicians, and at the present time the total number of recorded cases of tuberculosis of the thyroid gland is over 130. On reviewing these cases, however, it appears that there still is considerable confusion as to the criteria necessary to establish a definite diagnosis of tuberculosis of the thyroid gland. The diagnosis is questionable in a number of cases reported.

Because of the relatively infrequent involvement of the thyroid gland as compared with other organs in patients suffering from pulmonary tuberculosis, an immunity of the thyroid gland to the invasion of the tubercle bacillus was assumed by a number of clinicians. This is still the consensus of most investigators. Tuberculosis of the thyroid gland was produced experimentally by direct injection of suspensions of the bacilli into the thyroid artery by Torri⁷ in dogs, and into the carotid artery by Roger and Garnier⁸ in rabbits and guinea pigs. Shimodiara⁹ was able to show that the spleen, kidney, and testis were more easily infected than the thyroid gland in rabbits. No conclusive experimental evidence is available to date to explain this apparent resistance of the thyroid gland to invasion by the tubercle bacilli.

The sclerotic changes of the thyroid gland associated with atrophy found in necropsy material of patients having died of chronic pulmonary tuberculosis were first described by Morin;¹⁰ however, studies by Roger

This study was aided by a grant from the Comly Fund for Research of the Ohio State University.

Received for publication, Oct. 17, 1944.

and Garnier⁸ demonstrated that these changes in the thyroid gland were due to the toxemia of the tuberculous disease, rather than actual invasion of the gland by the tubercle bacilli. Kashiwamura¹¹ found similar sclerosing changes in the thyroids of patients having died of other chronic nontuberculous diseases.

In the overwhelming hematogenous dissemination of the tubercle bacillus in miliary tuberculosis, the thyroid, as do the other organs of the body, becomes the seat of tuberculous infection. However, since death occurs invariably in a short time, such infection of the thyroid does not present a clinical problem in diagnosis or treatment, and only post-mortem material is available for study. Such cases have been reported in the literature.¹²⁻¹⁴

The diagnosis of tuberculosis of the thyroid gland in the majority of cases reported in the literature was based on routine histologic examination of thyroid tissue removed at thyroidectomy. In only a few patients was such a diagnosis suspected preoperatively and the diagnosis in the largest number was goiter, both toxic and nontoxic, thyroiditis, or carcinoma. The age of these patients usually fell in the fourth and fifth decades, and examinations, particularly of their lungs, failed to reveal any evidence of pulmonary tuberculosis or tuberculous infection anywhere else in the body. At the time of operation there was, as a rule, diffuse enlargement of the thyroid with nodule formation, and the diagnosis during operation was essentially that of the preoperative diagnosis. The postoperative course was uneventful and in all these cases there was primary healing of the wound. The patients were discharged and the diagnosis of tuberculosis of the gland was made days later on the basis of the histologic changes found in the microscopic sections. Thus, at the time of the true diagnosis of the condition, no fresh tissue was available, and culture or guinea pig inoculation could not be performed. An attempt was made to demonstrate the tubercle bacilli in the fixed tissues, dissolving the tissue in antiformin, and after concentration, staining the material by the usual Ziehl-Neelsen method. Using this approach, Ruppaner¹⁵ was able to demonstrate tubercle bacilli in one of his three cases, while Hedinger¹⁶ reported having found tubercle bacilli in six of his seven cases. In this country, Mosiman⁴ used the same method but was not able to demonstrate the tubercle bacilli, although he found acid-fast particles which could be mistaken for tubercle bacilli; however, they did not exhibit the typical morphology. Others who attempted to demonstrate tubercle bacilli by staining of fixed tissues or extracting the tissue with the antiformin method, but were unable to do so, were Dinsmore¹⁷ in twenty-one cases, Rankin and Graham⁶ in twenty-one cases, and Jaffe¹⁸ in four cases. The diagnosis of tuberculosis of the thyroid gland in the majority of cases, then, was based on histologic findings and interpretation, rather than by demonstrating the tubercle bacilli.

The histologic picture reported as being diagnostic of tuberculosis of the thyroid gland was the finding of both interfollicular and intrafollicular giant cells resembling Langhans cells, lymphocyte and round-cell infiltration with fibrosis. Jaffe¹⁸ was the first to point out that the tubercle-like structures in these glands were the results of noninfectious focal involutional changes of newly formed and old follicles. Rienhoff¹⁹ and Seed²⁰ demanded the demonstration of the tubercle bacilli before a diagnosis of tuberculous infection of the thyroid gland could be made with certainty.

Direct extension of a tuberculous process from cervical lymph glands,²¹ muscles,² and trachea and larynx⁸ to the thyroid gland has been reported. Such cases are not of particular surgical interest, the pathology being demonstrated in post-mortem material. The diagnosis of tuberculosis of the thyroid in these cases was based predominantly on finding extensive tuberculosis in the lungs and other organs.

There have appeared in the literature reports of sixteen cases of tuberculous abscesses of the thyroid gland. These abscesses, as a rule, developed in normal thyroid glands and clinically were characterized by a slowly increasing fluctuant swelling in one lobe or isthmus. The treatment consisted of incision and drainage, and was followed by delayed healing of the wound or sinus formation. The aspirated pus, when smeared or cultured, contained tubercle bacilli, and the granulation tissue removed was composed of tuberculous granulation. Tuberculous abscess of the thyroid gland was occasionally associated with tuberculosis elsewhere in the body, although the primary source of the infection could not be found in all cases. The thyroid function was not altered prior to and following incision and drainage of the abscess.

CASE REPORTS FROM THE LITERATURE

In 1894, Schwartz²² reported the first surgically treated case of tuberculous abscess of the thyroid. His patient was a 30-year-old man with a swelling of the right lobe of the thyroid. The mass moved on swallowing and the larynx was deviated to the left. On incision pus was obtained which was sterile on the usual culture but acid-fast bacilli were demonstrated by guinea pig inoculation. The incision healed. No other foci of tuberculosis were reported.

Ivanoff²³ reported a probable case of tuberculous abscess in a 23-year-old man. A swelling had appeared three months previously over the right thyroid gland, which became fluctuant, and on incision pus was obtained. No attempt was made to find the tubercle bacilli, but since the patient died of miliary tuberculosis following the development of tuberculosis of the left ileum and knee ten months later, Ivanoff made a diagnosis of tuberculosis of the thyroid gland.

In a boy 2 years of age, Clairmont,²⁴ in 1902, found a walnut-sized tumor in the region of the isthmus which, because of obstructive symptoms, was incised and found to contain pus. Acid-fast bacilli were not

demonstrated; however, the tissue removed showed tuberculous granulation tissue. The wound healed with difficulty and a draining sinus persisted for months. There was no evidence of tuberculosis elsewhere.

In a 42-year-old man with pulmonary tuberculosis limited to the left upper lobe a fluctuant mass was found by Pupovac²⁵ and on incision pus was obtained from an abscess of the isthmus. The diagnosis was made on the basis of histologic examination. The wound healed promptly. There was no evidence of hyperthyroidism.

Corner,²⁶ in 1904, reported on a 9-year-old girl who had a fluctuant mass in the right thyroid with a hard left thyroid lobe. After incision and drainage the wound did not close and the patient died seven months later of tuberculous meningitis and miliary tuberculosis.

The diagnosis of tuberculosis of the thyroid gland in the case of Ledidard²⁷ may be questioned. A male of 21 years had a fluctuant mass in the right thyroid gland. On puncture, pus was aspirated which was sterile, but contained numerous giant cells. There was complete healing of the puncture wound and no recurrence of the tumor.

v.Schiller²⁸ was the first to make a diagnosis of tuberculosis of the thyroid gland during the operation on a patient with a cystic tumor of the left thyroid gland. This 17-year-old male had tuberculosis of the lungs. The pus obtained with incision of the cyst contained tubercle bacilli and was rich in iodine.

Lenormant²⁹ reported a case, in 1908, of a man 40 years of age, with tuberculous osteomyelitis of the trochanter. There was a fluctuant swelling of the isthmus of the thyroid, which on incision contained pus. A sinus persisted after the operation.

In 1910, Halstead³⁰ reported a case of tuberculosis of the thyroid gland in a 28-year-old woman. A swelling in the thyroid region ruptured spontaneously with the discharge of a large amount of pus. The lining of the abscess was composed of tuberculous granulation tissue. Acid-fast bacilli were not demonstrated.

Pollag,³ in 1913, reported two cases of tuberculosis of the thyroid with abscess formation in which tubercle bacilli were demonstrated on smear. The first case was that of a 59-year-old white woman who had had a goiter since childhood. On examination she was found to have tuberculosis of the right knee and also of the lungs. A goiter was present; however, a fluctuant mass in the isthmus was incised and pus obtained. The wound healed in six weeks. The second case was that of a 74-year-old woman who presented a fluctuant swelling of the right thyroid lobe. There was no evidence of tuberculosis elsewhere. On incision, grayish-brown pus was obtained. The wound did not heal for five months.

Jean³¹ made a diagnosis of tuberculosis of the thyroid gland in a man of 42 years, who presented a cystic swelling of the thyroid. On incision, pus was obtained but no acid-fast bacilli were demonstrated. The wound healed promptly. There was no tuberculosis found anywhere else in the body.

In 1929, Jones³² reported a man 64 years of age, who had a tumor the size of a walnut in the region of the isthmus. There were no symptoms of hyperthyroidism. A thyroidectomy was done and the tumor was found to be an abscess, the pus of which contained tubercle bacilli on guinea pig inoculation. The wound did not heal and ultraviolet radiation was used. The patient did not return for follow-up observations.

A patient of 26 years, with pulmonary tuberculosis and all the symptoms of a toxic goiter, was operated upon by Keynes in 1938.³³ The right thyroid contained an abscess and the pus on smear was positive for acid-fast bacilli. The abscess wall showed tuberculous granulation tissue. The patient made an uneventful recovery from the thyroidectomy.

In 1941, two cases of abscesses of the thyroid gland were reported by Hare and Simpson³⁴ from the Lahey Clinic. A woman of 65 years had a swelling of the left lobe of the thyroid which on incision drained pus containing gram-positive cocci but no growth on culture. The wound healed with difficulty and x-ray was used, with healing of the wound in eleven months. The second patient was a woman 30 years of age. There was swelling in the region of the isthmus. No toxic symptoms were present. Pus was drained from an abscess cavity, the wall of which consisted of tuberculous granulation tissue. No acid-fast bacilli were demonstrated. X-ray treatment was used to aid in the healing of the wound, sinuses persisting for eight months.

AUTHORS' CASE REPORT

M. J. (No. 424066), a 21-year-old Negro student nurse, was admitted to the Starling-Loving University Hospital, June 14, 1942, complaining of a painful swelling in her neck and of afternoon fever. Four months prior to admission she developed a small swelling on the right side of the neck which gradually increased in size and was associated with difficulty in swallowing. In March, 1942, routine x-ray examination had shown what was interpreted as an early tuberculous lesion of the left lung and the patient was advised to discontinue her activity and go on absolute bed rest. She had slight afternoon temperature elevation, but no other symptoms referable to the chest. There had been no cough and no weight loss. There was no family history of tuberculosis.

The patient was a well-developed Negro woman. The pulse on admission was 96, with a temperature of 99.4° F. The blood pressure was 138/86 mm. There was no lymphadenopathy. There was a round, fluctuant enlargement of the lower portion of the right thyroid lobe, while the isthmus and left lobes were normal in size and consistency. The cystic swelling of the thyroid did not transilluminate and it was freely movable, not attached to the skin or muscles. Examination of the chest revealed normal breath sounds and the heart was not enlarged.

The red blood count was 3,860,000, with a hemoglobin of 11.5 Gm. The white blood count was 6,200, with 78 per cent neutrophils, 18 per cent lymphocytes, 3 per cent monocytes, and 2 per cent eosinophiles. The sedimentation rate was 2.0 mm. per minute. The basal metabolic rate was minus 21 per cent and the blood iodine 5.1 micrograms per cent. X-ray films of the chest showed an area of increased density in the second interspace on the left side, which had all the appearance of a minimal tuberculous lesion. There was no excavation. The trachea

just below the larynx was deviated to the left. The urine was normal. Sputum examination did not demonstrate acid-fast bacilli.

A diagnosis of hemorrhagic cyst of the thyroid and pulmonary tuberculosis, minimal, apparently active, was made. Using cyclopropane and oxygen anesthesia, the thyroid was exposed through a low collar incision. The left lobe and isthmus of the thyroid were normal in size and appearance. The upper portion of the right lobe was normal while the lower portion was adherent to the adjacent structures, and in trying to mobilize it the capsule was broken into with the escape of a considerable amount of greenish-gray thick pus. Exploration with the finger revealed a large cavity with ragged wall which had replaced the lower portion of the left lobe of the thyroid. The wound was closed with drainage. The pus was sterile on usual culture and no organisms were seen. Guinea pig inoculation was done. The guinea pig died six weeks later of tuberculosis, acid-fast rods being found in the spleen, liver, and site of injection.

The wound did not heal and the patient was discharged to her home on absolute bed rest. Dr. Ralph Holmes of Chillicothe, Ohio, gave her eight x-ray treatments of 100 r. each at three-day intervals, to aid in the healing of the wound. Examination Nov. 14, 1942, revealed that the wound was closed, and x-ray examination of the chest showed the tuberculous lesion to be smaller. The patient was allowed gradual increase in her activity and when last examined, the lesion in her lungs had disappeared except for a small area of fibrosis in the second interspace. The patient returned to work in December, 1943, at which time there was no evidence of activity in her lungs. The basal metabolism, Feb. 1, 1944, was minus 10 and x-ray examination of the chest was reported as being normal.

DISCUSSION

Our case and the majority of those collected from the literature present the criteria necessary for the absolute diagnosis of tuberculosis of the thyroid gland, as advocated by Seed.²⁰ He states that a diagnosis of tuberculosis of the thyroid gland can be made with certainty only when tubercle bacilli are found, when there is definite necrosis or abscess formation, and when there is an etiologic focus in the body outside the thyroid gland. In the seventeen cases presented in this report, tubercle bacilli were demonstrated in seven. In Pollag's two cases the tubercle bacilli were found on direct smear, while v.Schiller and Keynes obtained positive cultures. Schwartz, Jones, and we demonstrated the acid-fast bacilli by guinea pig inoculation. In the other ten cases, the tubercle bacilli were not demonstrated; however, there is no report of an attempt having been made to find the bacilli. Apparently no smear was made, nor was there guinea pig inoculation or culture. However, the appearance of the pus and the absence of other organisms, with the histologic appearance of the removed tissue, was assumed sufficient proof to make a diagnosis of tuberculous abscess of the thyroid gland.

Four patients with tuberculous abscess of the thyroid gland also had tuberculosis of the lungs, which in all probability was the source of the infection, which, however, was not of sufficient severity to cause death. Only two of these patients, the one reported by Keynes and our case, were receiving treatment for the pulmonary tuberculosis. Four patients had tuberculous osteomyelitis and of these one died of miliary

tuberculosis several months after the drainage of the thyroid abscess: Corner's patient had cervical lymphadenopathy and died seven months later of tuberculous meningitis and miliary tuberculosis. No other foci of tuberculous infection were demonstrated in eight of the reported cases. Since routine x-ray examination of the chest was not used and no tuberculin test was made, these patients may be assumed to have had a primary focus which was not found on routine examination.

The treatment of tuberculous abscess of the thyroid consisted of incision and drainage in thirteen of the cases; one abscess ruptured and drained spontaneously, while a thyroidectomy was done in two cases. In the largest number of patients the wound healing was characterized by delayed wound healing and sinus formation lasting up to one year. Ultraviolet radiation was used by Jones and x-ray treatment by Hare and Simpson and us in an attempt to accelerate delayed wound healing. In six patients the wound healed by primary intention.

Definite goiter was present in three patients, one of which was toxic. The latter had a thyroidectomy with recovery. The amount of thyroid tissue destroyed by the tuberculous infection was not sufficient in these patients to cause postoperative hypothyroidism.

SUMMARY

A case of tuberculous abscess of the thyroid gland is reported, together with a brief outline of sixteen cases selected from the literature. Tuberculous abscess of the thyroid was equally distributed between males and females and the ages varied from 7 to 74 years. Three patients had definite goiters, of which one presented toxic symptoms. The clinical picture of tuberculous abscess was that of a cystic swelling of the thyroid gland of several months' duration, which on incision was found to contain thick pus, positive for acid-fast bacilli on smear, culture, or guinea pig inoculation. The tissue removed showed tuberculous granulation. There was delayed healing of the wound in the majority of cases. In no patient was postoperative myxedema demonstrated. A focus of tuberculous infection outside the thyroid gland was demonstrated in nine patients. Two patients died of miliary tuberculosis, while the others made uneventful recoveries.

REFERENCES

1. v.Rokitansky, K.: *Lehrbuch der pathologischen, Anatomie*, Vol. 3, ed. 3, Wien, 1859.
2. Virchow, R.: *Die krankhaften Geschwülste*, Vol. 3, 22 Vorlesung, 1864.
3. Pollag, S.: Ueber Tuberkulose der Schilddrüse, *Beitr. z. Klin. d. Tuberk.* 27: 159, 1913.
4. Mosiman, R. E.: Tuberculosis of the Thyroid, *Surg., Gynec. & Obst.* 24: 680, 1917.
5. Collier, F. A., and Huggins, C. B.: Tuberculosis of the Thyroid Gland, *Ann. Surg.* 84: 804, 1926.
6. Rankin, F. W., and Graham, A. S.: Tuberculosis of the Thyroid Gland, *Ann. Surg.* 96: 625, 1932.

7. Torri, O.: La tiroide nei morbi infettivi, Policlinico (sez. chir.) 7: 145, 1900.
8. Roger, H., and Garnier, M.: Des lesions de la glande thyroide dans la tuberculose, Arch. gén de méd., Par. 185: 385, 1900.
9. Shimodiara, Y.: Experimentelle Untersuchungen über die tuberkulose Infection der Schilddrüse, Deutsche Ztschr. f. Chir. 109: 443, 1911.
10. Morin: Physiologie et médication thyroïdiennes, Rev. méd. de la Suisse Rom., p. 241, 1895.
11. Kashiwamura, S.: Die Schilddrüse bei Infektionskrankheiten, Virchows Arch. f. path. Anat. 164: 373, 1901.
12. Chiari, H.: Ueber Tuberculose der Schilddrüse, Wien. med. Jahrb. 69: 119, 1878.
13. Fränkel, E.: Ueber Schilddrüsentuberculose, Virchows Arch. f. path. Anat. 104: 58, 1886.
14. Hegar, A.: Die Tuberculose der Schilddrüse, Disertation, Kiel, 1891.
15. Ruppenar, E.: Ueber tuberkulöse Strumen, Frankfurt. Ztschr. f. Path. 2: 513, 1909.
16. Hedinger, E.: Zur Lehre der Schilddrüsentuberkulose, Deutsche Ztschr. f. Chir. 116: 125, 1912.
17. Dinsmore, R. S.: Tuberculosis of the Thyroid Gland, S. Clin. North America 15: 885, 1935.
18. Jaffe, R. H.: Tubercle-like Structures in Human Goiters, Arch. Surg. 21: 717, 1930.
19. Rienhoff, W. F.: Tuberculosis of the Thyroid Gland, Ann. Surg. 96: 647, 1932.
20. Seed, L.: Goldberg, Clinical Tuberculosis, Ed. 2, Philadelphia, 1939, F. A. Davis Company.
21. Grasset, J., and Estor, E.: Myélite cervicale thyroïdite tuberculeuse, Rev. de méd. 7: 113, 1887.
22. Schwartz, C.: Abscès tuberculeux du corps thyroïde, Arch. de laryngol. 4: 1894.
23. Ivanoff: De la tuberculose de la glande thyroïde, Thèse de Lyon, 1899.
24. Clairmont, P.: Ueber Tuberculose der Schilddrüse, Wien klin. Wehnschr. 15: 1267, 1902.
25. Pupovac, D.: Zur Kenntniss der Tuberculose der Schilddrüse, Wien. klin. Wehnschr. 16: 1012, 1903.
26. Corner, E. M.: Primary and Secondary Local Tuberculosis of the Thyroid Gland, Tr. Clin. Soc. Lond. 37: 112, 1904.
27. Ledidard, H. A.: Primary Tuberculosis of the Thyroid, Tr. Path. Soc. Lond. 57: 153, 1905.
28. v.Schiller, K.: Kalter Abszess in der glandula thyroïdes, Wien. klin. Wehnschr. 2: 1088, 1908.
29. Lenormant: La tuberculose du corps thyroïde á propos d'un case d'abcès froid thyroïdien, Progrés méd. 24: 445, 1908.
30. Halstead, A. E.: Tuberculosis of the Thyroid Gland With Report of a Case, Internat. Clin. 1: 120, 1910.
31. Jean, G.: Tuberculose du corps thyroïde, Ann. d'anat. path. 3: 761, 1926.
32. Jones, B. T.: Tuberculosis of the Thyroid Gland, Am. J. Surg. 7: 629, 1929.
33. Keynes, G.: Tuberculosis of the Thyroid Gland, Lancet 235: 1357, 1938.
34. Hare, H. F., and Simpson, H. N.: Tuberculosis of the Thyroid Gland, Lahey Clin. Bull. 2: 123, 1941.

INTRASTERNAL INFUSIONS AND TRANSFUSIONS

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IN MILITARY and civilian medicine the treatment of shock is of paramount importance. Whether the condition is brought about by wounds, hemorrhage, or burns, the immediate physiologic results are the same, and there is an urgent need for the parenteral administration of fluids. These fluids can usually be given by vein, but in some instances the veins are collapsed, thrombosed, or absent, or the vein areas are obliterated by wounds or burns.

The bone marrow offers a ready channel for the administration of fluids in these cases, as first described by Tocantins.¹

The present report is a study of the administration of various fluid mediums through the sternal marrow. The work was done on routine patients in the general wards of a large city hospital.

The technique of sternal puncture and infusion is very simple. The needle used is $1\frac{1}{4}$ inch, 16 gauge Luer type with a stylet. The site of puncture is anywhere in the midline of the sternum but preferably in the region of the second or third interspaces.

A small spot of iodine is painted over the puncture site, novocain is injected into the skin, subcutaneous tissues, and periosteum, and the sternal needle is tapped into the marrow cavity by means of a small mallet. The mallet technique is superior to pushing the needle because perfect control is exercised and the danger of perforating the sternum and injuring the heart and great vessels is eliminated.

The stylet is removed and suction applied with a 10 c.c. syringe. Aspiration of bloody fluid proves whether the needle is in the marrow cavity. The infusion is then begun in the usual way.

Our series consists of thirty-five infusions of all types of fluids. The experimental data are given in Table I.

As seen from Table I, all fluids except blood ran in easily. That includes saline, glucose, sulfonamide drugs, insulin, serum, and plasma. Difficulties were encountered with blood and that in varying dilutions. This is hard to explain except on the basis of the size of the particulate matter in the blood in relation to the histologic structure of the marrow.

The internal structure of the sternum consists of spongy bone in which there are masses of cells traversed by thin-walled sinuses.

At sternal puncture the needle is driven through the outer body plate into the cellular mass in the interior of the sternum. It is plain to see how fluids not containing particular matter could traverse the cell masses and get into the capillaries much more easily than fluids con-

TABLE I

PUNC- TURE NUM- BER	AGE	SEX	DIAGNOSIS	SOLUTION	REMARKS
1	77	M	Virus pneu- monia	5% Dextrose in saline	2000 c.c. ran in well in 4 hr.
2	86	M	Virus pneu- monia	5% Dextrose in saline	1000 c.c. ran in well in 2 hr.
3	63	M	Myelogenous leucemia & virus pneu- monia	Whole blood citratcd	Unsuccessful; sternal needle in- serted, marrow withdraws eas- ily but solution would not run in
4	70	F	Gastric car- cinoma	5% Glucose in saline	3000 c.c. ran in well in 7 hr.
5	71	F	Carcinoma of head of pancreas	Whole blood citratcd	Unsuccessful; would not run in by gravity; 100 c.c. given by syringes with difficulty
6	73	F	Carcinoma of stomach	5% Glucose in saline	4000 c.c. ran in easily in 10 hr.
7	65	F	Diabetes mel- litus	5% Glucose in saline	2000 c.c. ran in easily
8	80	F	Carcinoma of stomach	5% Glucose in saline	2000 c.c. ran in easily
9	65	F	Diabetes mel- litus & hemiplegia	5% Glucose in saline	3000 c.c. ran in easily
10	73	F	Metastatic carcinoma	5% Glucose in saline	3000 c.c. ran in easily
11	73	F	Carcinoma of stomach	5% Glucose in saline; sulfa- thiazole, 5 Gm.; nicotinic acid, 100 mg.; Vit. B, 50 mg.; Vit. C, 200 mg.	3000 c.c. ran in easily
12	73	F	Metastatic carcinoma of stomach	5% Glucose in saline	2000 c.c. ran in easily
13	59	M	Carcinoma of rectum	5% Glucose in saline	2000 c.c. ran in easily
14	43	M	Carcinoma of rectum	Saline, 100 c.c.; whole blood citratcd, 23 c.c.	Saline ran in well; blood added, infusion stopped; needle washed out with saline, tried everything to get running again; unsuccessful
				Saline 100 c.c.; citratcd blood 100 c.c.	Needle reinserted 4 hr. later; blood diluted 50:50 with sa- line; ran in with great diffi- culty
				5% Dextrose in saline	3000 c.c. ran in well through same needle following unsuc- cessful administration of blood
15	43	F	Shock, temp. 107° F.	5% Glucose in distilled water plus Hart- man's solution	1000 c.c. ran in slowly except when respirations were deep and even, then it ran in quite rapidly
16	40	F	Anemia	Whole blood citratcd	100 c.c. saline ran in; stopped when blood was added; unsuc- cessful
17	44	F	Anemia	Saline, whole blood citratcd	100 c.c. saline ran in well; stopped when blood was add- ed; injected some with syringes with great difficulty

TABLE I—CONT'D

PUNCTURE NUM- BER	AGE	SEX	DIAGNOSIS	SOLUTION	REMARKS
18	70	M	Anemia, 20% Hb.	Saline with whole blood citrated	100 c.c. saline ran in then stopped when blood was added
19	70	M	Anemia	Whole blood citrated	Tried to inject forcibly with syringes; had to discontinue
20	36	M	Anemia	5% Glucose in saline	1000 c.c. ran in slowly
21	73	F	Carcinoma of esophagus	5% Glucose in saline	4000 c.c. ran in very well
22	64	F	Uremia	5% Glucose in saline; Sod. sulfathiazole, 7 Gm.	2000 c.c. ran in very well
23	73	F	Carcinoma of esophagus	5% Glucose in saline	3000 c.c. ran in very well
24	64	F	Pneumococ- cus menin- gitis	5% Glucose in saline; sulfa- diazine, 2 Gm.; anti- pneumonia serum, 100,000 U. type 8	3000 c.c. ran in very well
25	32	F	Postoperative shock	Saline and whole citrated blood	500 c.c. saline ran in well; 100 c.c. blood ran in slowly, then stopped
26	64	F	Pneumococ- cus menin- gitis	5% Glucose in saline	3000 c.c. ran in very well
27	38	F	Pneumonia	Whole blood citrated	Diluted 50:50 with saline; ran in too slowly, discontinued
28	70	F	Carcinoma of stomach	Whole blood citrated	100 c.c. forced in with syringes; discontinued as unsuccessful
29	60	F	Diverticulitis of colon	5% Glucose in saline	2000 c.c. ran in very well
30	60	F	Hemorrhage	Whole blood citrated	50 c.c. forced in with syringes; discontinued
31	72	M	Malnutrition, hypoprote- inemia	Plasma	Ran in very well
32	48	M	Cirrhosis of liver	Plasma	Ran in very well
33	49	M	Nephrotic syndrome	Plasma	Ran in very well
34	75	F	Anemia malignancy	Plasma	Ran in very well
35	62	F	Postoperative shock	Plasma	Ran in very well

taining cells, which would be caught by the sticky masses of primitive cells in the marrow and cause a blockage.

To prove that this was the case, saline was run into the sternum after the blood blockage had occurred, and it went in easily. To show that there was nothing wrong with the blood which would not go into the sternum, it was run into the same patient's vein.

In spite of the disappointment with blood, the sternal route of administering fluids and plasma is very satisfactory.

An interesting variation of technique has been developed in patients who have collapsed veins and need blood in addition to fluids. In these cases the fluids are first given by sternum until the circulation volume is increased to such a point that the veins again stand out. The blood transfusion is then given through the veins.

CONCLUSIONS

1. Intrasternal infusions of saline, glucose, and plasma are practical.
2. Intrasternal transfusions of blood were unsuccessful.
3. The sternal route is of great value in the treatment of shock.

The authors wish to thank Dr. T. Price, superintendent of City Hospital, for his cooperation in carrying out this work.

REFERENCES

1. Tocantins, L. M.: Rapid Absorption of Substances Injected Into the Bone Marrow, *Proc. Soc. Exper. Biol. & Med.* 45: 292, 1940.
2. Tocantins, L. M., and O'Neill, J. F.: Infusion of Blood and Other Fluids Into the Circulation Via the Bone Marrow; *Proc. Soc. Exper. Biol. & Med.* 45: 782, 1940.
3. Tocantins, L. M., O'Neill, J. F., and Price, A. H.: Infusions of Blood and Other Fluids Via the Bone Marrow in Traumatic Shock and Other Forms of Peripheral Circulatory Failure, *Ann. Surg.* 114: 1085, 1941.
4. Tocantins, L. M.: Infusions Through the Bone Marrow, *Clin. Med.* 49: 220, 1942.

TRENCH FOOT

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DURING the past winter many of our soldiers suffered from trench foot, a condition manifested by pain and swelling of the feet following exposure of the parts to wet and cold, usually in a trench or foxhole. The observations that follow are based on the study of 125 of these patients at a general hospital.

Trench foot, frostbite, immersion foot, shelter foot, and chilblain are closely related.¹ The main difference among these conditions is the manner of occurrence. The majority of our patients were suffering from trench foot, but there were two with immersion foot. The signs, symptoms, and course of the latter could not be distinguished from those of the patients with trench foot.

PREDISPOSING FACTORS

One or any combination of several factors seemed to produce the same signs and symptoms. These factors are as follows:

1. *Wet and cold.*—These men were exposed to the cold and wet of Italy. The average time of continuous exposure before reporting to sick call was eleven days. The extremes were two and forty days. The patients did not know exactly the temperature of the weather but they agreed that it was not extremely cold. They thought that the thermometer remained well above freezing during the day but there was some ice formation at night. Greene² has noted that trench foot was less common at extremely low temperatures than when the temperature was a little above freezing and the ground wet and muddy. Similarly, dry cold weather is better tolerated than is moist cold. Eight degrees Fahrenheit or lower is necessary to produce severe frostbite.

2. *Dependent Position of Feet and Circulatory Stasis.*—Most of these soldiers were in foxholes for long periods at a time, consequently their feet were in a dependent position day and night. Greene² has observed that people who developed the condition known as shelter foot, characterized by swelling of the feet, spent days and nights in the air raid shelters of London. During this time their feet were in the dependent position almost constantly and pressure was exerted on the popliteal fossae. Pressure might be an etiologic factor, as was suggested by the observation that those who sat with one leg crossed over the other developed swelling in the lower leg. A similar observation was made by us in some of our patients who had the disease worse in one foot

Received for publication, Dec. 23, 1944.

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than in the other. One reason that we could offer, in most cases, to explain this was their statement as to the position they assumed in the foxhole.

3. *Change of Socks*.—A better idea of continuous exposure is offered by the fact that the average time these patients went without changing their socks was seven days. The extremes were one and twenty-five days. The men said their socks were usually wet. All the patients were wearing light or heavy wool socks during the time of their exposure. Thirty per cent of the patients wore either combat shoes or galoshes.

4. *Previous Attacks*.—In this group of patients 8 per cent had had previous attacks of frostbite or trench foot, but in only three had these occurred during World War II. The others had had trouble five to fifteen years previously. Only one of these recurrent cases was severe.

5. *Previous Foot Injury*.—Eleven per cent had had previous foot injury but only in two patients was this factor thought significant. One of these developed gangrene in one foot (one year before, he had broken that foot and it still became swollen after long walks) but had no trouble with the other foot. The second patient was the only soldier in his company affected. He stated that the others had the same exposure. Two years previously he had had crushing injuries to both feet.

6. *Ringworm Infection*.—Fifteen per cent had epidermophytosis of their feet recently. These figures are about the usual incidence for all soldiers.

7. *General Condition*.—Seventy-five per cent of the patients were in good or excellent general condition when seen by us. The others were in fair condition as evidenced by their statements of an average loss of only ten pounds of weight since the beginning of exposure. We were unable to determine the presence of any specific vitamin deficiency. Kappert³ thinks there is a relationship between vitamin B deficiency and the development of frostbite but Stephenson and co-workers⁴ disagree. He notes that the swelling associated with vitamin deficiencies is usually not accompanied by pain, which symptom is the most common complaint of sufferers with trench foot.

SIGNS AND SYMPTOMS

The symptoms are well known. After exposure to wet and cold for a period varying from a few hours to several days, the man complains of painful and swollen feet. Pain was often the first symptom, but in many cases swelling of the feet and inability to get the shoes on after a change of socks was noted. Indeed, 8 per cent of the patients did not know they had trench foot until they were sent to an aid station for a wound or sickness. After becoming warm their feet became swollen and painful.

Other symptoms were numbness and burning. Most patients complained of hot feet and would ask that all covering be removed from their feet. A trench foot ward presents an unusual sight in January.

The feet of all patients are protruding from neatly turned back covers. Only 15 per cent stated that at no time during the course of their disease did they feel better with their feet in the cool air.

Sweating and coldness were late symptoms which did not appear during the early part of the disease. At least three of the patients who were returned to duty complained of no late symptoms except profuse sweating of the feet.

All of the patients gave a history of having had swelling of the feet at some time during the first part of their illness. Sixty per cent had edema which persisted for more than three weeks. Some degree of pinking or ecchymosis accompanied this edema in most instances.

In 25 per cent of all the patients, pulsation in the dorsal pedal artery, posterior tibial artery, or both was absent. We were unable to determine a relationship between such finding and the severity of the disease, although the pulsations did seem stronger in the hot feet and weaker in the cold feet. Pulsations of these vessels are not always palpable in normal feet.

Most of our patients were seen one to two weeks after the beginning of hospitalization, therefore in many instances the first formation of blisters could not be observed. When these were present on arrival in this hospital, the vesicles contained either a clear or a sanguineous fluid and were similar in appearance to the descriptions of those occurring in high altitudes frostbite as given by Davis and others.⁵

In 9 per cent of our patients the degree of vesiculation was severe and in these cases the outcome was like that described by Davis and associates.⁵ The skin dried, turned black, and dropped off, sometimes en masse. The affected toes were finally covered with thin, smooth, shiny, tender skin.

Six per cent of the patients developed a type of dry reaction which was similar to that seen in high altitude fliers. The tissues were shriveled, desiccated, and black. The affected part of the toe or toes would drop off, usually within six to eight weeks. Those patients who presented vesicle formation and persistent swelling of the feet and whose temperature varied frequently seemed to suffer more than those who had loss of toes.

SKIN TEMPERATURE

During their hospital stay, readings of skin temperature, usually the knee, shin, foot, and toe, were taken with an accurately calibrated skin thermometer. Often these readings were repeated on one or more occasions. Since it was not feasible to use a constant temperature room, an attempt was made to take readings when the room temperature was between 62 and 70° F. After the legs of the patient had been exposed for one-half hour, the usual "normal" temperature on the back of the foot varied from 70 to 80° F. and on the ball of the big toe from 60 to 70° F.

The patients of our group were seen usually from one to four weeks after the onset of their trouble and at this time the feet with the most damage were the warmest. Frequently the temperature of the injured foot and toe would be the same, contrary to the normal, and often above 85 or 90° F. Palpation of the feet would frequently lead to a statement of the relative degree of injury between the two feet because of a temperature difference. Where the trench foot was mild in degree, the skin temperature of the feet and toes often dropped to "normal" in one or two weeks. Usually the temperature was increased in the swollen feet; however, this was not true in some cases with swelling three and four months after injury. When damage was severe and gangrene of the toes was present, the temperature of the affected foot and base of the toes remained elevated almost without exception until after separation of dead tissue.

While skin temperature recordings were an aid in judging the condition and early course in the disease, they were of little value in the late cases in which the patients complained of sensitivity to cold. The skin temperature response of five such patients who had moderately severe trench foot of from seventeen to forty days' duration was studied simultaneously with five normal controls. These men were on beds with their legs exposed and were not allowed to move about. Skin temperature readings were made every hour for seven hours. The temperature of the room was 62° F. at the start and 68° F. at the end of the test period. The temperatures of the exposed legs, feet, and toes reached their lowest point about three hours after exposure, and the curves of the drop in the trench foot cases showed no significant variation from that of the normal. In other words, the response of the arterial sympathetics on exposure to temperatures of 62 to 68° F. was not different in "recovering" trench foot and in normal cases. Whether these damaged feet respond differently to lower temperatures, we did not observe.

PATHOLOGIC AND LABORATORY OBSERVATIONS

In an attempt to find a pathologic basis for the persistent symptoms in some patients without gangrene, skin biopsies were taken from one foot in three patients and from both feet in a fourth, about ninety days after onset of symptoms. All complained of persistent swelling, pain on walking, and occasional bluish discoloration. Control tissue was taken (post mortem) from four patients who had normal feet. All tissue was removed from the dorsum of the foot and consisted of full thickness of skin, with varying amounts of subcutaneous tissue. Sections were stained with hematoxylin eosin and with Mallory's aniline blue stain for collagen.

As White and Warren⁶ have observed, the outstanding change in the tissues was an increased formation of collagen. This was most marked in the papillary layer of the dermis and surrounding the small blood

vessels in the dermis as a whole. The vessels, particularly of the papillae, were more numerous and appeared dilated, suggesting a more active capillary circulation. These vessels showed no evidence of thrombosis or constriction by the surrounding fibrous tissue. There was slight to moderate perivascular round-cell infiltration in all sections, which was not observed in the control tissues. A small amount of collagen formation was present diffusely throughout the dermis, although this layer showed no increase in thickness over that seen in the controls.

The epidermis was essentially normal in all sections. There was no significant smoothing of the rete pegs and the basal layer did not show the irregularity and indistinct arrangement noted by others.

Histologic determination of the presence of edema was uncertain. In the one patient in whom both feet were biopsied, it was not possible to determine by section which was the clinically edematous foot. Both feet had been edematous, but at the time of biopsy only one was swollen.

There was neither significant pathologic change in nerves nor marked fibrosis surrounding nerve trunks. The skin appendages were normal in number in three sections and slightly decreased in the other two. Histologic examination was made on gangrenous tissue removed from one patient, but this showed no changes not entirely characteristic of any dry gangrene, regardless of cause.

Sedimentation rates by the Westergren method and the presence of cold agglutinations were determined routinely in most patients. In only one patient was the sedimentation rate increased (± 10 mm.). In all others the rates covered a range between 0.5 and 3 mm. per hour. Cold agglutination was determined on saline washed red cells at a temperature of approximately 5° C. Since the determination of agglutinin titer was not practical, the results were recorded in terms of completeness of agglutination, 3 and 4 plus being those in which 75 to 100 per cent of the cells were clumped. Readings on twenty-two normal controls were made under the same conditions. Thirteen per cent of eighty-four patients with trench foot and 4.5 per cent of the control group showed 3 or 4 plus agglutination. If the basis for significant agglutination is broadened to include those patients showing 50 per cent of cells clumped, then 35.6 per cent of patients with trench foot and 22.6 per cent of the controls had agglutination of 2 plus or more. There was poor correlation between these findings and the degree of edema in nongangrenous feet, however, all patients who had gangrene and on whom determinations were made showed positive agglutination. The significance of these findings is nevertheless uncertain.

TREATMENT

The treatment employed in this hospital was simple. The patients were grouped for treatment purposes into mild, moderate, and severe types. Those with a mild type were kept in bed three to fourteen

days. The feet were slightly elevated if there was any pain. A modified type Buerger's exercise was begun when the pain and swelling had diminished. As soon as possible the patients with no signs were encouraged to walk, first without shoes and later with their regular shoes. When they were able to walk one-half mile and soak their feet alternately in hot and cold water without return of symptoms they were ready for discharge to duty or to a convalescent hospital, depending on the toughness of their feet.

The same plan was followed with the group of patients who were moderately affected. The rest period was longer and the exercise more graduated. They were given the same tests before being returned to duty.

All groups were given multivitamin capsules and large doses of vitamin B as recommended by Kupperl.³

Patients of the first two groups recovered without residual signs and symptoms but, as will be seen, it was necessary to hospitalize some patients for three months or longer before returning them to duty.

The treatment of the severe type was more of a problem. Twenty per cent were in this group. Blebs were opened under sterile precaution and sulfanilamide crystals used freely. Dry dressings were always applied. Necrotic tissue was cut off or washed away with saline solution at room temperature. The feet with gangrenous areas were treated the same way. There was no severe infection in any of these patients. None had a temperature of more than 100° F. at any time during their course in the hospital.

Brambel and Loker⁷ have suggested the use of dicoumarin to check the spread of gangrene from frostbite. None was used in this series; since we have not found the gangrene progressive, we cannot see the value of either decoumarin or heparin.

The gangrenous parts were allowed to drop off and no skin grafting was necessary. In two patients it was necessary to cut off the protruding ends of bones of the toes. None of the patients with bleb formation received additional tetanus toxoid or antitoxin. None developed tetanus although tetanus has been reported following frostbite.

Pain, and in some instances swelling, was relieved by cooling. Usually exposure to the cold air of December and January of North Africa was sufficient. Davis and others⁵ have found that the results obtained in the treatment of cases of frostbite at room temperature were as good or better than that of those treated by continued cooling. Ungley⁸ and Greene⁹ have reported good results using a dry refrigerator. Most writers on this subject advocate cooling by one method or another. Six of our patients whose pain was not relieved with ordinary cooling were improved by the use of ice bags. Two patients who were seen early in our experience were interesting. They had only slightly swollen feet but they complained of severe pain. When they were not

relieved of their pain by ordinary cooling they were given buckets of ice water and allowed to cool their feet. They received immediate relief of the pain but after several treatments the feet became swollen and blue. This form of therapy was discontinued. For those with more intense pain and severe swelling we now use dry cold in the form of protected ice bags and we have had no increase in the edema since the dry cold was used.

We have had little experience with sympathetic block in the treatment of this condition. It was tried without benefit on three patients with persistent pain and swelling of the feet. One patient said his feet hurt more. The only indications we can see for sympathetic block or sympathectomy would be, as Patterson¹¹ has described, for feet that remained cold with absent pulsations of the large arteries of the feet or possibly in that group of patients left with an unstable vasomotor system in the feet. However, these people feel better when their feet are cold than when they are hot. We would recommend careful study before performing a sympathectomy.

RESULTS

Trench foot, even in the milder cases, proved to be disabling. Those patients who were able to return to duty were hospitalized for an average of sixty-one days, with the extremes at 30 and 115 days. Eighty-two per cent (counting those who were referred to a convalescent hospital) were able to return to duty. Eighteen per cent were returned to the Zone of the Interior. Of this number three had a peculiar condition manifested by one or more of the following: severe swelling, sudden changes in the temperature of the feet, pinking or ecchymosis, pain and tenderness of the feet, and stiff toes sometimes with a toe drop. For lack of a better term we have called this condition chronic trench foot, as Theis¹² has described a chronic frostbite.

PROPHYLAXIS

Prophylaxis is important and methods for it have been published in Army journals.¹³ The following considerations are of sufficient importance to warrant repetition:

1. The clothing and diet should be adequate.
2. Socks should be changed frequently.
3. Feet should be elevated as much as possible.
4. The feet should be exercised regularly. Greene reports on foot drill as employed in the trenches in 1918. During this exercise each man inspected his neighbor's feet and rubbed them in oil.
5. Socks and shoes should be removed at the first sign of swelling.
6. If trench foot is suspected there should be no rubbing with or without snow.
7. Sudden warming is dangerous.

SUMMARY AND CONCLUSIONS

The symptoms, clinical course, and possible etiologic factors in 125 cases of trench foot are presented. The patients were studied in a general hospital one to four weeks after the onset of their disease.

In the Italian Campaign this condition caused extensive disability. In those patients returned to duty, the average period of hospitalization was sixty days. Eighteen per cent required evacuation to the Zone of the Interior.

From observation of this group of patients, it appears that this is a condition caused primarily by ischemia due to capillary constriction resulting from long exposure to cold. This reaction is intensified by wet, stasis, and pressure. The continued ischemia produces varying degrees of capillary damage which upon the resumption of active circulation is manifested by edema and increased heat. In certain cases where edema persists, chronic inflammation with diffuse terminal fibrosis occurs and in more severe cases nonprogressive dry gangrene develops.

Simple conservative treatment with encouragement to walk at the earliest possible time seems to give the best results. Amputation of gangrenous parts was not necessary in any of these cases.

Prevention is probably not possible in all cases but education of the individual soldier in foot care, and the provision of loose, dry footgear should minimize the occurrence of this condition.

REFERENCES

1. Schaefer, C. L., and Sanders, C. E.: Pernio (Chilblains), *J. Missouri M. A.* 38: 159, 1941.
2. Greene, Raymond: Frost Bite and Kindred Ills, *Lancet* 2: 689, 1942.
3. Kappert, A.: Contribution to the Clinical Treatment of the B-Hypovitaminosis, *Schweiz. med. Wehnschr.* 28: 874, 1943, as translated by W. F. Prior Company, Inc., Hagerstown, Md.
4. Stephenson, S., Mast, W., and Shronts, F.: First Aid Treatment for Certain Conditions Common Among Shipwreck Survivors, *Hosp. Corps Quart.* 16: 1, 1943.
5. Davis, Loyal, Scarff, E., Rogers, Neil, and Dickinson, Meredith: High Altitude Frost Bite, *Surg., Gynec., & Obst.* 77: 561-575, 1943.
6. White, C., and Warren, Shields: Causes of Pain in Feet After Prolonged Immersion in Cold Water, *War Med.* 5: 6, 1944.
7. Brambel, E., and Loker, F.: Application of Dicoumarin in Trauma and Gangrene, *Arch. Surg.* 48: 1, 1944.
8. Ungley, C. C.: Treatment of Immersion Foot by Dry Cooling, *Lancet* 1: 681, 1943.
9. Greene, Raymond: Cold in the Treatment of Damage Due to Cold, *Lancet* 2: 695, 1942.
10. Webster, D. R., Woolhouse, F. M., and Johnston, J. L.: Immersion Foot, *J. Bone & Joint Surg.* 24: 785, 1942. (See also References 4, 8, and 9.)
11. Patterson, H.: Effect of Prolonged Wet and Cold on the Extremities, *Bull. U. S. Army M. Dept.* 75: 62, 1944.
12. Theis, W.: Frostbite of Extremities, *Arch. Phys. Therapy* 21: 663, 1940.
13. Office of the Surgeon General: Trench Foot, *Bull. U. S. Army M. Dept.* 74: 46, 1944.

OBSERVATIONS ON THE TREATMENT OF EMPYEMA THORACIS WITH PENICILLIN

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WHEN the sulfonamide drugs became available, the various derivatives were tried, both locally and systemically, in the treatment of empyema thoracis. Accumulated data on this problem prove that the almost universal use of the sulfonamide drugs for pneumonia has resulted in a marked decrease in the incidence of purulent pleurisy.¹⁻³ There is equally convincing evidence, however, that once pus has formed in the pleura neither the general nor the local administration of the sulfonamide drugs can be relied upon to effect a cure.⁴ Toxic side actions preclude sufficiently large doses of the drug by systemic routes to influence materially an empyema after it has formed, and the local injections of the various sulfonamide drugs into the pleura have failed because their antibacterial action is inhibited when they are mixed with pus.

With the introduction of penicillin, interest has been revived in the nonsurgical treatment of empyema. Penicillin not only has a strong antibacterial action when given systemically, but also retains its potency in the presence of blood and pus. Moreover, this remarkable agent has a proved low toxicity for man and enormous doses can be employed, both parenterally and locally, without dangerous or distressing side effects. It appears, therefore, that penicillin is ideal for local injection into an empyema cavity, and when combined with systemic treatment a cure might be effected without surgical drainage when the infection in the pleura is caused by penicillin-vulnerable organisms. This optimistic outlook on the treatment of a hitherto surgical condition is substantiated by Tillett, Cambier, and McCormack,⁵ who report eight patients with pneumococcal empyemas treated by intrapleural injections of penicillin. In seven, the infection was eliminated by local therapy without surgical drainage; six recovered completely; and one patient with pyopneumothorax has a persistent pneumothorax, but the pyothorax has cleared satisfactorily. One patient, who in the opinion of these authors had insufficient initial treatment, suffered a relapse and required surgical drainage. Bennett and Parkes⁶ report four cases. In one, a seropurulent, sterile effusion complicated a staphylococcal pneumonia. They believe this represented an early empyema aborted by sulfonamide therapy. A single injection of 20,000 units of calcium penicillin caused the

local condition to disappear. Three other cases are described, two of which had collections of seropurulent fluid in the pleura containing beta hemolytic *Streptococcus*. Two local injections of penicillin caused the fluid to become sterile and cures seemed to be accomplished. The amount of penicillin given is not recorded. The fourth patient, a baby, had a massive *Staphylococcus empyema*. Systemic and local treatments with penicillin were employed and these authors state that after ten days of treatment the patient is convalescent and clinical and roentgen evidences "indicate that there will be no residual disease of lungs and pleura."

Undoubtedly as penicillin becomes generally available, more successful, nonsurgical cures of empyema will be described. This communication includes experiences with twenty-four cases of empyema. Thirteen patients received both systemic and local treatments; in five cases, intrapleural injections of penicillin were employed alone; and in six cases, only systemic administration of the drug was utilized. A much larger series of cases of empyema with chronic draining sinuses resulting from war wounds, which were operated upon with penicillin protection, are not included. The problems in this group are entirely different.

Important data are summarized in Table I.

It is evident that there is considerable variation in the amounts of penicillin given in each case and when intrapleural injections were employed there was no uniformity in the dosages or in the intervals between local administrations. The initial treatment in all but four cases was begun in other hospitals and the patients were referred to the Thoracic Surgery Section, Walter Reed General Hospital, after the acute phase of the disease had subsided. This accounts for the lack of a standard therapeutic plan.

The results from giving systemic injections of penicillin alone are summarized in Table II. Intramuscular injections were employed in all cases. In one case, Case 2, Table II, intravenous injections were also utilized.

SYSTEMIC ADMINISTRATION OF PENICILLIN

The results in only six cases are of little statistical value. The clinical impressions gained by studying this small series, however, are of some importance. One patient, case 3, Table II, would probably have died if large amounts of penicillin had not been given. It is interesting that only one positive culture was obtained from the pus in the empyema cavity after penicillin therapy was started. Local penicillin was not recommended because the fluid became sterile. The pus thickened rapidly, however, and required drainage. In this case, penicillin controlled a widespread *Staphylococcus* infection of the lungs. The empyema was relatively unimportant. In Cases 2, 4, and 5, Table II, the cultures of the pus were not altered but serious illnesses were converted into relatively innocuous ones by controlling the pulmonary lesion.

TABLE I
SUMMARY OF ENTIRE GROUP

CASE	PENICILLIN UNITS		OTHER MEDICATION	ORGANISM	RESULT	REMARKS
	LOCAL	GENERAL				
1	160,000	2,000,000	Serum Sulfadiazine	Pneumococcus type V	Thoracostomy; cure	Local penicillin daily for 4 days, 40,000 U. doses; operation 14 days after penicillin therapy started; pus became sterile but continued to form
2	460,000	None	Sulfadiazine	Hemolytic	Str. Chronic empyema required radical operation	Local penicillin given over period of 6 days, four doses of 100,000 U., followed by two injections of 30,000 U.; operation 17 days after penicillin therapy started; pus became sterile, lung would not re-expand, had broncho-pleural fistula
3	150,000	None	Sulfadiazine	Hemolytic	Str. Thoracostomy; cure	Local penicillin, initial dose 20,000 U., 7 days later, 75,000 U.; 7 days later 50,000 U.; operation 48 days after therapy started; pus temporarily sterilized but organisms reappeared; original size of empyema cavity 2,000 c.c.
4	360,000	8,250,000	Sulfadiazine	Beta Str.; Staph. albus	Apparently cured without operation	Five intrapleural injections, two 100,000 P. doses and three 40,000 U. injections, over a period of 24 days; systemic penicillin therapy from March 1 to July 1, 1944; pus became sterile
5	100,000	None	Sulfadiazine	Beta hemolytic Str.	Thoracostomy; cure	Single dose of 100,000 U. of penicillin intrapleurally; operation 2 months after penicillin therapy; pus became sterile but drainage was necessary to evacuate it
6	240,000	400,000	Sulfadiazine	Hemolytic	Str. Thoracostomy; cure	Three doses of 70,000 U. and one injection of 50,000 U. of penicillin intrapleurally on 4 consecutive days; operation 4 days after penicillin therapy completed; pus became sterile and very thick
7	125,000	350,000	Sulfadiazine	Pneumococcus type V	Thoracostomy; cure	Local penicillin given on 3 consecutive days, operation 5 months later; after penicillin therapy, pus was sterile on culture most of the time; occasional positive cultures

8	80,000	4,160,000	Sulfadiazine	Hemolytic Str.	Thoracostomy; cure	40,000 U. penicillin, two doses in 3 days; operation 2½ months after penicillin therapy; pus sterile at intervals but thickened, and organisms re-appeared.
9	150,000	5,480,000	None	Beta Str.	Two operations to obliterate a chronic empyema cavity	Penicillin injected intrapleurally on 3 consecutive days; operation 4 months after penicillin therapy begun; pus in empyema cavity became sterile after the first injection of penicillin
10	600,000	930,000	Sulfadiazine	Anaerobic hemolytic Str.	Thoracostomy day of admission	Eight injections of intrapleural penicillin over period of 9 days; putrid pyopneumothorax, undrained for three weeks
11	30,000	2,840,000	Sulfadiazine	Hemolytic influenzae	Thoracostomy; cure	Organisms not vulnerable to penicillin; no effect on disease
12	110,000	685,000	Sulfadiazine	Hemolytic Str.	Thoracostomy; cure	Local penicillin on 4 consecutive days; operation 25 days after penicillin started; culture not effected by local penicillin
13	125,000	2,720,000	Sulfadiazine	Hemolytic Str.	Thoracostomy cavity not healed	Nine injections of local penicillin over a period of 21 days; operation 38 days after appearance of pleural fluid; after local penicillin most of cultures negative with organism visible on smear occasionally
14	100,000	770,000	Sulfadiazine	Hemolytic Str.	Apparently cured without operation	A single dose of 100,000 U. of penicillin intrapleurally; 3½ months' hospitalization; fluid remained clear, straw-colored and became sterile
15	150,000	None	Sulfadiazine	Staph. albus	Thoracostomy; cure	Local penicillin: initial injection of 50,000 U., 11 days later, 100,000 U.; operation 2 months after penicillin therapy started, pus became sterile
16	200,000	None	Sulfadiazine	Pneumococcus type V	Thoracostomy; cure	Local penicillin on 4 consecutive days; operation 1 month after penicillin started; pus became sterile but thickened and continued to form

TABLE I—CONT'D

CASE	PENICILLIN UNITS		OTHER MEDICATION	ORGANISM	RESULT	REMARKS
	LOCAL	GENERAL				
17	220,000	2,450,000	Sulfadiazine	Hemolytic Str.	Thoracostomy; cure	Local penicillin: 40,000 U. at 10-day intervals followed by 40,000 every other day for 3 days; operation 45 days after treatment begun; pus thick and sterile, had irrigations with saline
18	120,000	1,800,000	Sulfadiazine	Hemolytic Str.	Thoracostomy; cure	Three injections of 40,000 U. of penicillin intrapleurally on consecutive days; culture temporarily sterilized, operation 1 month after empyema found
19	None	670,000	Sulfadiazine	Unknown	Chronic sterile empyema; radical operation	Penicillin and sulfadiazine given before culture of fluid was established; sputum cultured hemolytic Str. 2 months from formation of fluid until operation
20	None	1,695,000	Sulfadiazine	Pneumococcus type I	Thoracostomy; cure	Empyema developed while patient was on penicillin therapy; total hospitalization 45 days; postoperative period 28 days
21	None	2,400,000	Sulfadiazine	Staph. aureus	Thoracostomy; cure	One positive culture showing Staph., all others negative; pus very thick, postoperative period 34 days
22	None	525,000	Sulfadiazine	Pneumococcus type XIX	Thoracostomy; cure	No effect on pus
23	None	720,000	Sulfadiazine	Hemolytic Staph. aureus	Thoracostomy; cure	No effect on cultures; massive empyema cavity, cavity healed in 60 days
24	None	640,000	Sulfadiazine	Nonhemolytic Str.	Apparently cured without operation	One culture of nonhemolytic Str.; all others sterile; fluid turbid but never thick

TABLE II

THE EFFECTS OF SYSTEMIC ADMINISTRATION OF PENICILLIN IN EMPYEMA

CASE	UNITS OF PENICILLIN	ORGANISM	COMMENT AND RESULT
1	670,000	Hemolytic Str. (?) in sputum	Penicillin and sulfadiazine given before an organism was found in pleural fluid; chronic sterile empyema requiring radical operation
2	1,695,000	Pneumococcus type I	Empyema developed while patient was receiving 25,000 U. of penicillin at 3-hour intervals
3	2,400,000	Staph. (?)	Thick pus found; one positive culture showing Staph.
4	525,000	Pneumococcus, type XIX	No effect on culture
5	720,000	Hemolytic Staph. aureus	No effect on cultures; massive empyema cavity
6	640,000	Nonhemolytic Str.	One culture of nonhemolytic Str., all others sterile; fluid turbid but never thick; apparently cured without drainage

The intramuscular administration of penicillin in large amounts will apparently inhibit the growth of bacteria in some infected effusions. This occurred in three of the six cases recorded. It is apparent, however, that this will not eliminate the necessity of removing frank pus from the pleura when it has formed. It is probable, however, that frequently pleural exudates which contain polymorphonuclear leucocytes and represent potential empyemas will remain sterile and be absorbed as a result of systemic penicillin therapy.

The results in patients treated with only intrapleural injections of penicillin are reviewed in Table III.

TABLE III

THE EFFECTS OF LOCAL PENICILLIN ON EMPYEMA

CASE	UNITS OF PENICILLIN	ORGANISM	COMMENT AND RESULT
1	460,000	Hemolytic Str.	Pus became sterile; chronic, sterile empyema requiring radical operation
2	150,000	Hemolytic Str.	Pus temporarily sterilized; cure after thoracotomy
3	100,000	Beta hemolytic Str.	Pus became sterile; drainage necessary because pus became very thick
4	150,000	Staph. albus	Pus became sterile on culture; operation necessary to evacuate thick pus
5	200,000	Pneumococcus type V	Pus became sterile; operation to remove thick sterile pus

INTRAPLEURAL PENICILLIN

Intrapleural injections of penicillin caused the disappearance of penicillin-vulnerable organisms from the pus in the empyema cavities of every patient so treated. Surgical drainage was performed in all of the cases in this group because the pus became so thick that removal by needle aspiration was difficult. Doubtless if more vigorous and frequent efforts had been made at needle aspiration, thoracostomy might have been avoided in some of these cases.

In two patients, the pleura was irrigated with saline solution to thin the exudate in an effort to make the aspirations more effectual. In both cases the pus was finally removed by surgical drainage.

All of the five patients who were treated with local penicillin alone had received sulfadiazine during the pneumonic stage of the disease. Intrapleural injections of penicillin had been started before the patient was referred to us. Since their general conditions were good and the pneumonias controlled, general administration of penicillin was omitted. It is our opinion, however, that the systemic administration of the drug should accompany local therapy.

COMBINED SYSTEMIC AND LOCAL PENICILLIN THERAPY

The results from the combination of systemic administration and intrapleural injections of penicillin are included in Table I, Cases, 1, 4, 6 to 14, 17, and 18. The obvious advantage of employing both routes is that the intramuscular or intravenous penicillin treatment is probably more effectual against the suppurative inflammation and pneumonic phases of the disease, whereas local injections of the drug may sterilize quickly the contents of the empyema cavity.

It is important to emphasize again, before discussing the effects of local and systemic penicillin on empyema thoracis, that it is possible that in some of our cases in which the pus became sterile, repeated thoracenteses may have eliminated the necessity for surgical drainage. The reasons for our reluctance to delay operation will become evident as the various cases are discussed.

In ten of thirteen patients treated with both intrapleural and systemic penicillin, the pleural fluids became sterile. In two patients, cases 7 and 8, Table I, organisms reappeared. In case 12, Table I, 110,000 units of penicillin, intrapleurally, on four consecutive days, did not cause hemolytic *Streptococcus* to disappear from the empyema cavity; 685,000 units of intramuscular penicillin were also given to this patient. The fluid in Case 11, Table I, was infected with *Hemophilus influenzae* and was not influenced by combined penicillin therapy. It is interesting that Tillett and his associates⁵ describe a case in which thick pus, containing *Pneumococcus*, type XIX, and *Hemophilus influenzae* became sterile on culture after the introduction of intrapleural penicillin. Fleming's observations have indicated that *Hemophilus influenzae* is

not susceptible to the antibacterial action of penicillin. Tillett and co-workers⁵ conclude that the high concentration of penicillin in the pleura or perhaps a strain of *Hemophilus influenzae* unusually susceptible to penicillin may account for their success.

Two penicillin cures are included in cases in which the patients received both intrapleural and general administration of the drug, and one patient developed chronic empyema while on combined therapy. These cases are presented later in the discussion.

The majority of the patients in this group had thick pus in the pleura when they were referred to Walter Reed General Hospital. Surgical drainage was performed to remove the pus without regard of its temporary sterility. In Cases 7, 8, 13, and 17, Table I, the period of hospitalization was prolonged unnecessarily because evacuation of the pus from the pleura was delayed, presumably because it was sterile.

COMMENT

Penicillin Cures.—Three patients escaped surgery. These cases deserve detailed consideration.

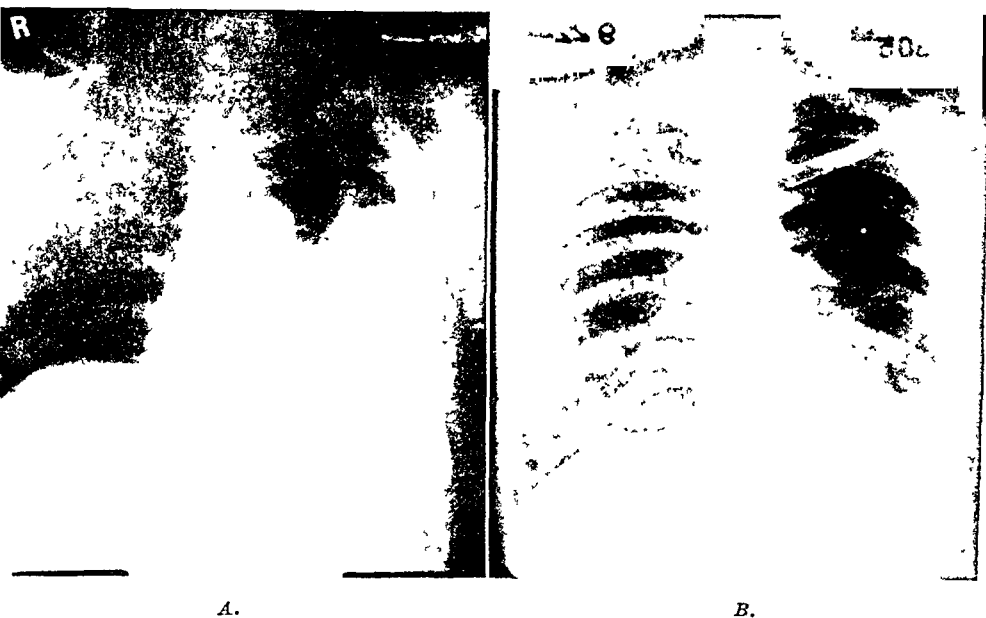
CASE 4 (Table I).—The patient developed a pleural effusion about one week after the onset of pneumonia. Cultures revealed *beta Streptococcus* and *Staphylococcus albus*. Five intrapleural injections of penicillin were given over a period of twenty-four days. Two initial doses of 100,000 units were followed by three injections of 40,000 units. The fluid removed by a thoracentesis is described as creamy brown. A total of 5,525 c.c. of this material was evacuated from the pleura by needle aspiration. The patient received intramuscular penicillin from March 1, 1944, until July 1, 1944. The pus became sterile after the first injection of intrapleural penicillin. A grand total of 330 intramuscular injections of penicillin (8,250,000 units) and eleven thoracenteses is a dear price to pay to avoid surgical drainage of an empyema cavity. Add to this six months of hospitalization and the nonsurgical cure loses its attractions (Fig. 1).

CASE 14 (Table I).—The second penicillin cure was accomplished in a patient who developed pneumonia which was first treated with sulfadiazine. On the fifth day of the illness, straw-colored fluid containing hemolytic Streptococci was aspirated from the chest. Systemic penicillin was begun and a single injection of 100,000 units of penicillin was given intrapleurally. The fluid remained clear and became sterile. Hospitalization was not prolonged and penicillin was discontinued as soon as the temperature, hemogram, etc. remained at normal limits for a week.

Critical analysis of this case indicates that this is not an example of an abscess being cured by penicillin, but rather it illustrates the value of local penicillin therapy in aborting an empyema. Pus was never present in the pleural cavity. Failure to make a clear and precise discrimination between an infected serous or serohemorrhagic fluid and a true, fully developed abscess of the pleura accounts for much of

the confusion in the past literature on the treatment of empyema. If this error is carried into the discussion of the value of penicillin in the treatment of empyema thoracis, observations on this phase of the subject will be of little value.

CASE 24 (Table I).—The patient had pneumonia which was treated with sulfadiazine. After sulfonamide therapy the temperature subsided and improvement continued for ten days, followed by a recurrence of high fever. Fluid was found in the right pleura and 400 c.c. of cloudy yellow fluid were removed by thoracentesis. Cultures revealed a nonhemolytic *Streptococcus*. Penicillin by the intramuscular



A.

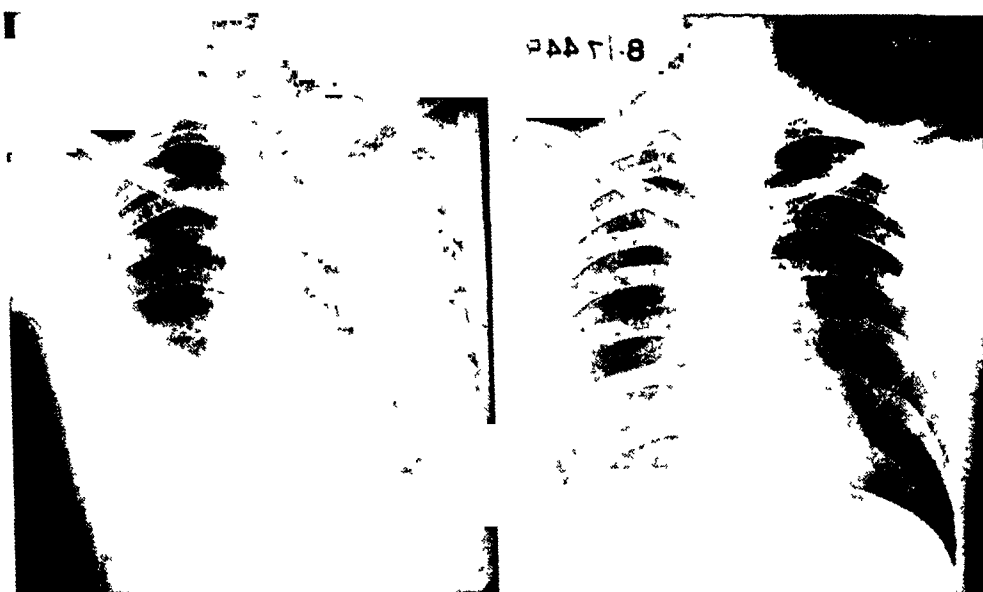
B.

Fig. 1.—A, Appearance of empyema after treatment by repeated aspirations and penicillin therapy was started. B, Roentgenogram four months later. The empyema seems to be cured by conservative management.

route was started the day before the fluid was discovered. A second thoracentesis, three days later, revealed sterile, turbid fluid which on smear contained 18,000 white blood cells with 100 per cent polymorphonuclear leucocytes. Intramuscular penicillin was continued for ten days. The fluid disappeared and the patient is fully recovered. No intrapleural penicillin was employed. This probably represents another example of the prevention of abscess formation in the pleura (Fig. 2).

Penicillin Sterile Chronic Empyemas.—There were three patients with chronic, sterile empyemas in the group of twenty-four cases. No new clinical spectacle was presented. They were the same gaunt, apathetic, hungerless individuals characteristic of old-fashioned, neglected empyemas of prepenicillin days. The chest wall is retracted, atrophy of disuse is evidenced in the puny muscles of the thorax, and the mechanical problem of cavity obliteration remains to be solved.

CASE 2 (Table I).—It is safe to conclude that penicillin therapy was extremely beneficial in Case 2. The patient developed an empyema complicated by a large bronchopleural fistula and was treated by closed drainage elsewhere before he was transferred to Walter Reed General Hospital. Three weeks after the original operation, wide dependent drainage was established. The fistula closed and the empyema cavity diminished in size. Healing progressed until the original 1,500 c.c. cavity measured 300 c.c. and then remained stationary. Radical surgical intervention was necessary to obliterate this cavity. The benefits of penicillin were confined to the control of a severe streptococcal pneumonia, which could easily have been fatal in the absence of penicillin therapy. There was probably no effect upon the complicating, purulent pleuritis



A

B

Fig. 2—A, Roentgenogram of chest. The fluid was infected with *Streptococcus E.* sixteen days later. Two large collections of fluid in the right chest. B, Appearance of chest sixteen days later. Two large collections of fluid in the right chest. The cultures of the fluid became sterile without intrapleural injections of penicillin. 1 systemic penicillin therapy were employed.

CASE 9 (Table I).—In Case 9, local and systemic penicillin was employed. The pus in the empyema cavity became sterile after the first intrapleural injection. The operation for the removal of the thick pus was delayed for four months, presumably because the cultures remained sterile. By this time the pleura was thickened and two operations were necessary to obliterate the cavity. Two thousand cubic centimeters of pus were removed at the first operation. Twelve thoracenteses had been performed during the trial of penicillin therapy. A total of 6,175 c.c. of fluid was aspirated from the chest during this same period (Fig. 3).

This is another example of carrying a good thing too far.

CASE 19 (Table I).—The patient became ill suddenly and had clinical and roentgen evidence of pneumonia. Fluid formed in the pleura, and systemic penicillin was employed before a culture of the fluid was obtained. The fluid remained sterile and consequently the true nature of the infection was never established. When the patient was referred to us there was a collection of thick, jellylike, sterile material in the pleura. It was impossible to remove it by needle aspiration. After careful studies to rule out the possibility of tuberculosis as an etiologic factor, the chest was opened and the organized, semiliquid mass was removed. The partially collapsed lung was splinted by a heavy layer of fibrous tissue, and it was necessary to perform a decortication operation to effect expansion of the lung.

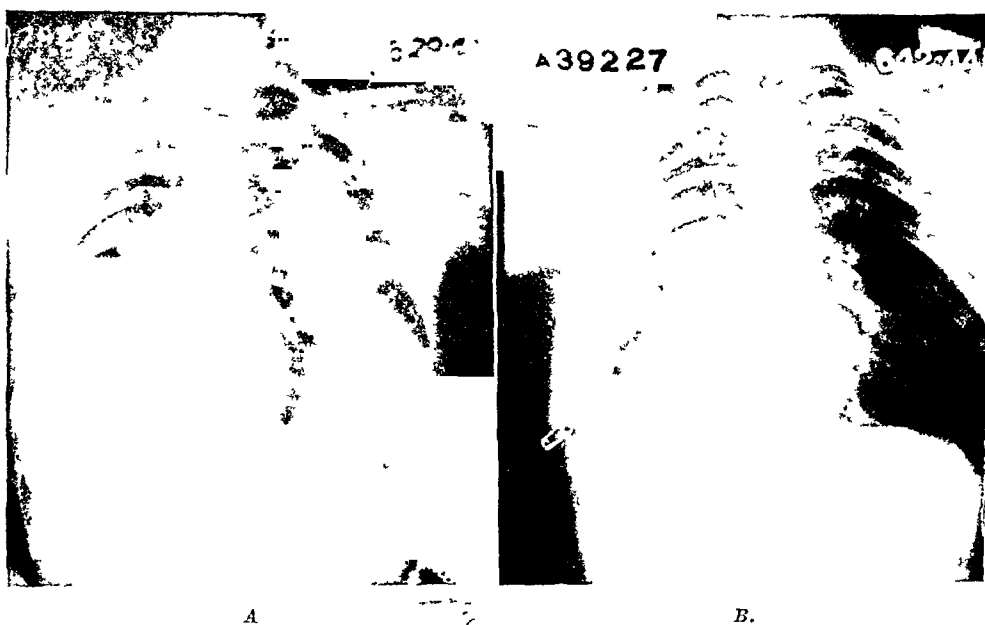


Fig. 3—A, Roentgenogram of chest showing large empyema. Surgical drainage had been delayed four months because the pus remained sterile after local and systemic administration of penicillin. B, Appearance of the chest after surgical drainage to remove thick sterile pus; note thickened pleura. A second operation was necessary several months later to obliterate the cavity completely.

If vigorous attempts had been made to aspirate the sterile fluid from the pleura while it was still thin and the lung had re-expanded, a radical operation in this case would not have been necessary. The principal difficulty appears to be that a sterile empyema was erroneously considered as a cured empyema (Fig. 4).

Pyopneumothorax.—The pyopneumothorax treated by Tillett and co-workers,⁵ in which the pyothorax was controlled but the pneumothorax persisted, has already been described. It seems unlikely that their patient is really cured. Fortunately, the infection responded to penicillin. In instances of putrid pyopneumothorax resulting from the rupture of a



A.



B.



C.

Fig. 4.—A, The roentgen appearance of a chronic sterile empyema. B, Photograph of empyema cavity when it was opened at operation. C, Photograph of the puttylike sterile pus in the cavity.

lung abscess into the pleura, however, there is not only the problem of infection, but the immediate threat to life from altered intrapleural pressure.

CASE 10 (Table I).—Case 10 furnishes an example of the overenthusiastic use of penicillin. The patient developed a pyopneumothorax. The pleura contained foul-smelling pus and cultures revealed anaerobic hemolytic *Streptococci*. A putrid infection of the pleura was treated by intramuscular penicillin, intrapleural penicillin, and sulfadiazine. Surgical drainage was delayed for three weeks (Fig. 5). Even in a mixed putrid infection of this type, penicillin may have some beneficial effects by altering or inhibiting some of the organisms growing in symbiosis with the common anaerobic bacteria usually responsible for necrotizing infections of the lungs. To delay drainage in this type of case, however, in the vain hope that penicillin or any other agent will effect a cure, indicates a complete lack of understanding of fundamental surgical principles.



Fig. 5—Roentgenogram of pyopneumothorax resulting from the rupture of a lung abscess into the pleura. The pus was putrid and contained anaerobic *Streptococci*. Drainage was delayed three weeks while local and systemic penicillin therapy was tried.

DISCUSSION

Before the importance of penicillin in the treatment of empyema can be evaluated intelligently, it is apparently necessary first to define empyema, second to enumerate the criteria for determining when an empyema is healed, and third to review the recognized fundamental principles of the treatment of empyema of prepenicillin times.

Definition of Empyema.—Empyema is defined by both Webster and Gould,^{8, 9} as pus in a cavity, especially the pleural cavity. It is appar-

ent that serous or vaguely defined fluids should not be considered true abscesses of the pleura, and if cures are effected with penicillin they may represent aborted empyemas, but should not be considered as examples of nonsurgical cures of a mature abscess. It seems incredible that a sterile empyema could be considered a cured empyema, yet disastrous procrastination in cases in which the pleura was filled with sterile pus has occurred in several of our cases.

Graham¹⁰ has repeatedly emphasized the importance of distinguishing between infected effusions and fully developed abscesses of the pleura, in fact, the successful management of suppurative pleurisy depends upon this distinction. Premature open drainage of an infected effusion during the formative stage of an empyema exposes the patient to the dangers of interference with normal intrathoracic pressure relationships. Conversely, evacuation of thick pus must be performed early enough to prevent chronicity. Even when the pus of a pyogenic infection has been temporarily sterilized by chemotherapy, the problem of obliteration of an abscess cavity will remain to be solved. If this fundamental principle is accepted, it is essential to establish criteria to determine when an empyema cavity is really healed.

When Is an Empyema Healed? An empyema cavity cannot be considered cured until the cavity itself is obliterated. There is only one thoroughly reliable method to determine this, namely, by actual measurements of the cavity itself. Roentgenograms of the chest are helpful but experienced radiologists are aware that fairly large amounts of fluid may not be visible on ordinary roentgenographic examinations. For example, Rigos¹¹ has pointed out that in roentgenograms taken in the upright position, effusions of less than 400 c.c. are often difficult to detect. It is apparent, therefore, that improvement in the roentgenographic appearance of the chest following penicillin therapy for empyema does not necessarily constitute positive proof of a cure. Experienced surgeons are fully aware of the possibilities of recurrence of an empyema months or even years after the original illness. The term "cure" should be used with considerable caution, particularly when so-called nonsurgical measures of local injections and aspiration of the empyema are employed. In these cases accurate measurements of the cavity are impossible to obtain, and clinical and roentgenographic evidence may be temporarily misleading.

Fundamental Principles of Treatment of Empyema Thoracis.—During World War I, in connection with the activities of the Empyema Commission, Graham and Bell¹² outlined the principles for the treatment of empyema. The introduction of the sulfonamide derivatives has in no way altered their conclusions. It is important to re-examine these principles and to determine whether or not penicillin therapy will effect them. The two most important principles are, first, not to create an open pneumothorax during the time pneumonia is present; and second,

cause cultures of the fluid in the chest to become sterile. Intrapleural injections of penicillin will temporarily sterilize an empyema cavity in the great majority of cases. It is our impression, however, that combined systemic and intrapleural administration is desirable because the combined routes effect both the pulmonary and pleural lesions.

Probably penicillin will be extremely effectual in aborting empyema formation, but once pus is formed, and continues to form, even if sterile, the problem of cavity closure cannot be ignored. If healing is not rapid with disappearance of pus when conservative measures are employed, it is our opinion that surgical drainage is mandatory. Failure to observe the fundamental principle of adequate drainage of any pyogenic empyema, even if the pus is rendered temporarily sterile by penicillin, will invite the serious complication of chronicity. This occurred in two of twenty-four cases which we have observed. It should again be emphasized that the introduction of penicillin has not altered in any way the fundamental principles of treatment of empyema; only the details are changed.

As experiences with penicillin therapy accumulate, the therapeutic approaches will become more standardized. Based upon our own observations, a tentative working plan is suggested:

1. That an injection of intrapleural penicillin be given as soon as infected fluid appears in the pleura. It is important that local treatment be withheld until the organisms in the fluid are identified. This precaution will prevent waste of penicillin in infections which do not respond to the drug. An initial positive bacteriologic diagnosis will also rule out the possibility of a tuberculous effusion or empyema which may deserve consideration if no other bacteria are found.

2. If systemic penicillin has not been employed during the pneumonic stage of the disease, it should be combined with the local therapy. It might be argued that by the time an empyema becomes evident the pneumonic phase of the disease will have subsided and, therefore, systemic administration of penicillin would be superfluous. Florey and Cairns¹⁶ have emphasized the advantages of combined administration of penicillin in severe war wounds. The chief advantage of the systemic route is that the blood will contain a bacterial inhibitory substance which may control a spreading cellulitis or invasive infection. It is our opinion that the same principle is sound in the management of pneumonia complicated by empyema. This is particularly true in cases of streptococcal or staphylococcal empyema.

- 3: Probably three injections of 50,000 units of penicillin on alternate days are sufficient for local treatment. Before the penicillin is injected into the pleura, as much pus or infected fluid as possible should be removed by thoracentesis.

4. If pus continues to form and thicken, surgical drainage should be established. A *sterile* empyema is not a *cured* empyema, and evacuation

of frank pus should not be unduly delayed because organisms cannot be found after the penicillin treatment has been started. Our experiences confirm the statement included in the report of the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council, by Keefer and associates,¹⁵ namely, that even when the pus in an empyema cavity is sterilized by penicillin it often becomes so thick that thoracostomy is necessary to furnish adequate drainage.

As an adjuvant to skillful surgery, penicillin has already revolutionized the management of many surgical diseases of the thorax. In their excellent paper on *Major Complications of Penetrating Wounds of the Chest*, D'Abreu, Litchfield, and Hodson¹⁷ give a brilliant account of the value of the mold both as a prophylactic and as a therapeutic agent. There is every reason to predict that with "penicillin protection" the dangers of practically all operations upon the chest will be reduced. This communication is not intended to depreciate the value of this remarkable agent, but to emphasize that it will not afford protection from violations of the fundamental principles of surgery.

REFERENCES

1. Hurwitz, Samuel, and Stephens, H. Brodie: *J. Pediat.* 14: 11, 1939.
2. Schwartz, Louis, Flippin, H. F., and Turnbull, W. G.: *Ann. Int. Med.* 13: 2038, 1940.
3. Garvin, Curtis F.: *Arch. Int. Med.* 66: 1246, 1940.
4. Burford, T. H., and Blades, Brian: *J. A. M. A.* 118: 950, 1942.
5. Tillett, Wm. S., Cambier, M. J., and McCormack, James E.: *Bull. New York Acad. Med.* 20: 142, 1944.
6. Bennett, T. I., and Parkes, T.: *Lancet* 1: 305, 1944.
7. Fleming, A.: *Brit. J. Exper. Path.* 10: 226, 1929.
8. Webster's New International Dictionary, Springfield, Mass., 1943, G. & C. Merriam Company, Publishers.
9. Gould's Medical Dictionary, edited by Scott, R. J. E., and Brownlow, C. V.: Philadelphia, 1935, The Blakiston Company.
10. Graham, E. A., Singer, J. J., and Ballou, H. C.: *Surgical Diseases of the Chest*, Philadelphia, 1935, Lea & Febiger.
11. Rigos, Frank J.: *Radiology* 36: 568, 1941.
12. Graham, E. A., and Bell, R. D.: *Am. J. M. Sc.* 156: 839, 1918.
13. Cole, W. H., and Elman, R.: *Text Book of General Surgery*, Chapter on Thoracic Surgery, New York, 1944, D. Appleton-Century Company, Inc.
14. Keller, Wm.: Personal Communication.
15. Keefer, C. S., Blake, L. G., Marshall, E. K., Lockwood, J. S., and Wood, W. B.: *J. A. M. A.* 122: 1217, 1943.
16. Florey, M. E., and Cairns, H. A.: *Brit. M. J.* 2: 755, 1943.
17. D'Abreu, A. L., Litchfield, J. W., and Hodson, C. J.: *Lancet* 2: 197, 1944.

Three important papers which were not available when this manuscript was prepared are:

- Butler, E. C. B., Perry, Kenneth M. A., and Valentine, F. C. O.: *Treatment of Acute Empyema With Penicillin*, *Brit. M. J.* 2: 171, 1944.
- Nicholson, W. F., and Stevenson, C. R.: *Intrapleural Penicillin in Penetrating Wounds of the Chest*, *Brit. J. Surg.* 32: 176, 1944.
- D'Abreu, A. L., Litchfield, J. W., and Thomson, Scott: *Penicillin in Treatment of War Wounds of the Chest*, *Brit. J. Surg.* 32: 179, 1944.

COMPLICATING FACTORS IN THE SURGICAL MANAGEMENT OF VARICOSE VEINS

WITH SPECIAL REFERENCE TO INTERRUPTION OF SYMPATHETIC
NERVE IMPULSES AS AN ADJUNCT IN TREATMENT

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SUCCESSFUL results in the treatment of varicose veins of the legs depend upon complete obliteration of the principal components of the superficial venous circulation, the great saphenous system. Elimination of such an extensive venous network requires radical measures and it is to be emphasized that best results can be obtained only by a radical surgical technique.

Although numerous technical procedures have been developed through the years, only two have survived critical evaluation to the present time. The first is high ligation and division of the great saphenous vein combined with retrograde chemical sclerosis of the entire vein and its main tributaries. The operative technique of this procedure has been described in adequate detail¹⁻⁹ and needs no further elaboration except for one technical feature which deserves special mention. Sclerosis of the saphenous vein and its tributaries must be complete. Accomplishment of this important detail can be assured by employing the segmental sclerosis method of Pratt.¹ By this procedure, thorough sclerosis of the entire saphenous vein, from ankle to groin, can be obtained by passing a ureteral catheter a distance of 40 to 60 cm. down the distal venous segment after division of the main trunk at the fossa ovalis. The sclerosing agent is injected continuously as the catheter is withdrawn slowly upward, thus inducing thrombosis throughout the entire venous trunk. The advantage of catheterization is obvious: the common sclerosing materials act quickly and become rapidly fixed at their point of contact with the intima, so that retrograde injection at the fossa ovalis by needle or cannula results in obliteration of only a short segment of vein in the thigh, incomplete effect being exerted below the knee. Catheterization need not be confined to the main saphenous vein but may be applied to large tributaries as well. Such a maneuver involves the use of large quantities of sclerosant, as much as 30 c.c. of sodium morrhuate solution being injected into a single extremity.

The second method is the Mayo technique, consisting of the actual removal of long venous segments after stripping the varicosities free from their subcutaneous attachments. While not widely employed in

recent years, it has been carefully evaluated lately by Grimson¹⁰ in a large series of patients with gratifying results.

A high percentage of satisfactory results can be achieved by the combined ligation-division and massive sclerosis method of treatment. Certain complicating factors may be encountered, however, which interfere with the performance of an ordinarily simple operation and which may prolong or harass the convalescence. It is these complications in the treatment of varicose veins with which the ensuing discussion is concerned.

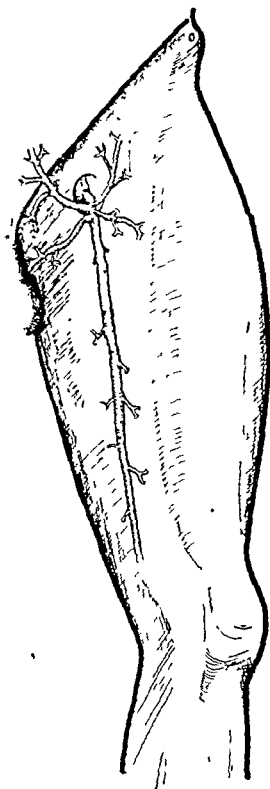


Fig. 1.—The usual anatomic pattern of four saphenous tributaries at the fossa ovalis.

ANATOMIC VARIATIONS

Anomalies of venous channels are common. From the standpoint of the great saphenous vein, three varieties in particular deserve mention: First the irregularity of relationships of the tributary channels at the fossa ovalis, second the occasional occurrence of an abnormally low saphenofemoral junction, and third the presence of tortuosity of the vessels.

Tributaries.—Normally, the main saphenous vein receives four well-defined venous trunks at, or very near, its entrance into the deep femoral vein (Fig. 1). These branches in most instances join the saphenous superficial, or external, to the fossa ovalis and, hence, super-

ficial, to the fascia lata. Ligation, division, catheterization, and retrograde sclerosis of each individual tributary, as well as the main saphenous vein itself, are important technical steps in the prevention of recurrences and can be done easily as long as the normal anatomic pattern prevails. Occasionally, however, anomalies of location place certain contributory trunks deep within the fossa ovalis itself. Such an arrangement complicates the operation by making the abnormal branches difficult to visualize to the extent that they may be entirely overlooked in the dissection. Case 1 illustrates this problem.

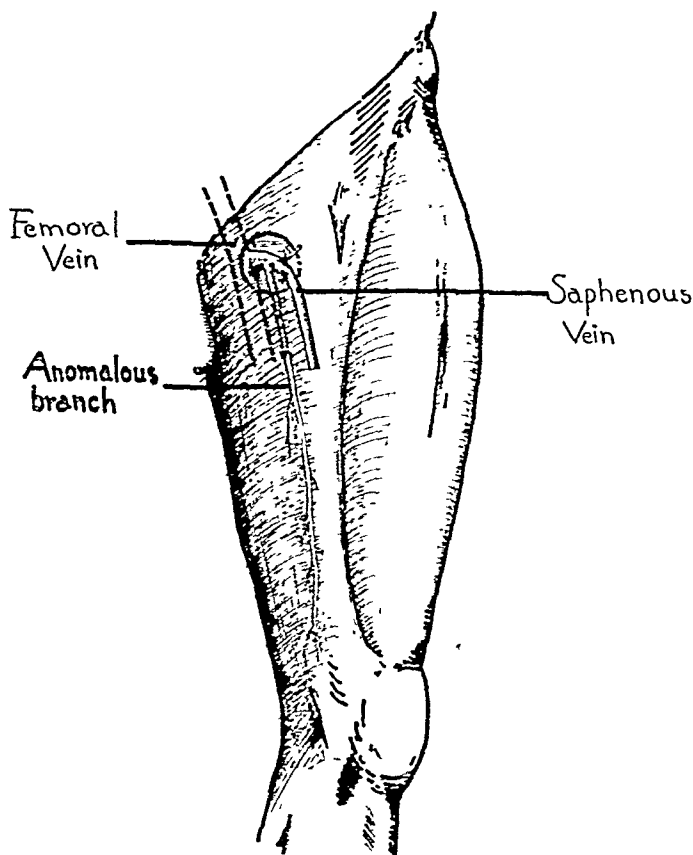


Fig. 2.—Anomalous anatomic arrangement showing one large tributary entering saphenous vein deep to fascia lata (see Case 1).

CASE REPORTS

CASE 1 (Roper Hospital No. 23262).—A 43-year-old Negro woman entered the hospital in October, 1943, presenting an indolent, fibrotic ulcer on the medial surface of the lower third of her right leg. Varicose veins were well defined and the history revealed that inadequate treatment had been attempted some eight years previously. After routine preoperative study by tourniquet tests, ligation-division and catheter injection of the saphenous vein were done at the fossa ovalis and just above the knee. During the dissection in the region of the saphenofemoral junction, it was noted that only two tributaries were demonstrable. After division of the superior margin of the fascial ring constituting the fossa ovalis, an

abnormally situated venous trunk was seen to enter the saphenous vein almost flush with the saphenofemoral torcula (Fig. 2). This was divided close to its point of entrance into the saphenous vein and its distal segment was catheterized in the usual manner. Palpation failed to detect the presence of the catheter in the upper 15 cm. of the thigh, but below this level the catheter could be palpated lying immediately beneath the skin. Such a situation indicated that the anomalous branch, although a part of the varicose saphenous system, was located deep to the fascia lata in the upper portion of the thigh, as illustrated in Fig. 2. Ligation, division, and retrograde sclerosis of the anomalous vessel and the other principal superficial trunks resulted in prompt healing of the ulcer.

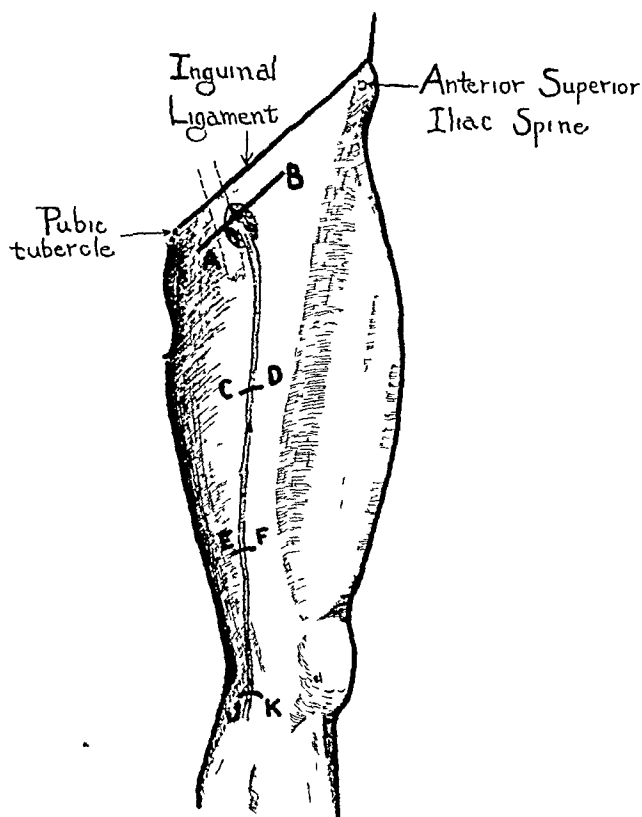


Fig. 3—*AB* represents routine transverse incision for exposure of saphenofemoral junction. *CD*, *EF*, and *JK* represent sites of election for re-exposure of saphenous vein when necessitated by obstruction to catheterization (see Case 3).

Low Saphenofemoral Junction.—In the great majority of patients, the main saphenous vein enters the femoral vein, via the fossa ovalis, about one inch below the inguinal ligament. As illustrated by Case 2, an abnormally low junction sometimes occurs. This variation can be annoying to the operator who prefers a transverse incision (Fig. 3), but of less significance when a vertical incision is made (Fig. 4); in either case, the existence of such an anomaly is confusing.

CASE 2 (Roper Hospital No. 20175).—A 26-year-old white medical student was admitted in June, 1943, because of massive saphenous varicosities of both legs, without pigmentation or ulceration. After preliminary tourniquet studies, each

leg was operated upon by the ligation-division and injection technique. Because of the tremendous degree of involvement, two procedures were carried out three days apart. A transverse incision was made in the left thigh one inch below and parallel to the medial one-half of Poupart's ligament. The fascia lata was exposed throughout the entire field, but the saphenous vein could not be located after careful search. Thereupon the fascia lata was divided vertically and the femoral vein was brought into view. By following this vessel distally the saphenous vein was found to enter at a point three and one-half inches below the level of the incision, strong downward retraction of the lower edge of the wound being necessary to expose the junction. The operation was then completed in the routine manner. An excellent result was obtained in each leg and the patient subsequently passed a military physical examination with ease.

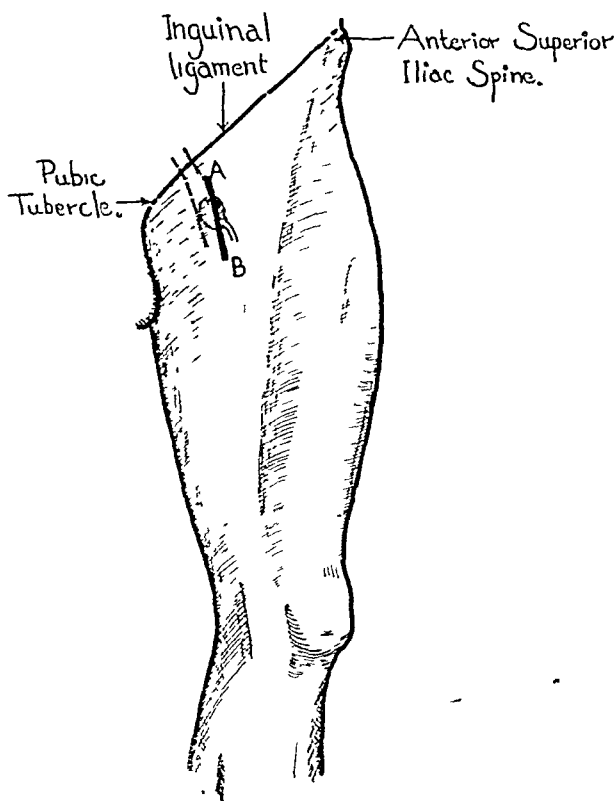


Fig. 4.—Vertical incision for combined high saphenous ligation-injection and femoral periarterial sympathectomy (see Case 7).

Extreme Tortuosity.—A complicating factor of considerable magnitude is the presence of marked tortuosity and multiple sacculations of the main saphenous vein. As previously stated, complete obliteration of the principal components of the saphenous system is the only guarantee of cure of varicose veins. If this is to be accomplished by injection of sclerosing material, virtually the entire intimal lining of the saphenous trunk and its largest tributaries must be subjected to contact with the thrombosing substance employed. Such an accomplishment is rendered difficult by the presence of tortuosity. When injec-

tion by needle or cannula is attempted, the greater intimal surface created by the existence of numerous saccular dilatations causes pooling and fixation of the sclerosing solution in a short high segment of vein and prevents dissemination distally from the point of injection. When catheterization is employed for the purpose of segmental sclerosis, arrest of the catheter usually occurs in the tortuous channel and its downward progress is halted. This difficulty frequently can be overcome by reversing the usual technique and re-exposing the saphenous trunk in the calf or at the knee (Fig. 3). Having done so, the venous channel is catheterized from below upward and the catheter usually can be made to appear at the point of saphenous division in the groin incision. Segmental sclerosis is then accomplished by slow, steady injection as the catheter is withdrawn gradually downward along the saphenous vein. Any remaining uninjected segments of the main venous trunk are treated in a similar manner until complete sclerosis has been obtained.

CASE 3 (Roper Hospital No. 19046).—A 45-year-old white woman was admitted May 31, 1943, for treatment of extensive bilateral varicose veins. After the usual preoperative evaluation of her deep venous circulation and arterial status, each leg was treated by the combined ligation-division and injection technique at separate operations five days apart. The procedure was uneventful in the case of the right leg, but tortuosity and sacculation of the left main saphenous were pronounced and caused arrest of the catheter 5 cm. from the fossa ovalis. To quote from the operative record, "so the latter (great saphenous vein) was re-exposed by a transverse incision just above the medial condyle of the knee (Fig. 3). The catheter was then passed upward from the knee and the entire segment of saphenous from femoral junction to knee was injected with 10 c.c. of sodium morrhuate." The remaining varicosities below the knee were then injected by catheterization to the ankle. The patient recovered uneventfully and is now judged to be cured.

COMPLICATIONS AMENABLE TO TREATMENT BY INTERRUPTION OF SYMPATHETIC NERVE IMPULSES

In recent years, the role of the sympathetic nervous system in disorders of the peripheral circulatory apparatus has received increasing attention. Regarding certain complications of varicose veins, sympathetic nervous activity is intimately concerned as a part of the pathologic process in three specific instances: (1) vasoconstriction, (2) pain of vascular origin, and (3) local hypoxia. Each of the following complications is characterized by one or more of these three autonomic nervous factors and each can be improved or completely abolished by interruption of the regional sympathetic impulses.

Thrombophlebitis.—In 1940, Ochsner and DeBakey¹¹ emphasized the strong element of vasospasm in the presence of acute inflammatory obstruction of the deep veins of the lower extremity. It is now generally accepted that the presence of inflammatory thrombosis, or even perivascular inflammatory reaction without actual venous obstruction, in-

initiates reflex vasoconstrictor impulses which are mediated by the sympathetic nervous system. Reflex impulses of autonomic origin tend to be discharged *en masse*. As a result, the vasoconstriction initiated by a femoral thrombophlebitis is widespread in the affected extremity and involves veins as well as arteries. Abolition of the vasospasm results promptly when novocaine infiltration of the lumbar ganglionated sympathetic chain is performed.

Spontaneous idiopathic thrombophlebitis is common in varicose veins, usually involving the main saphenous in its entirety or in either the thigh or leg segments. Accompanying signs of inflammation are prominent, consisting of redness along the distribution of the vein, increased local heat, and a palpable swelling of the involved segment. Pain is variable but is generally present and sometimes may be severe. Edema of the extremity may be a feature. In the presence of such a process, the methods of treatment of the varicosities vary from the usual routine procedure. In so far as it is possible, treatment should be directed toward obliteration of the saphenous tree as well as toward the thrombophlebitis. The latter condition presents two problems—prevention of embolism and control of the painfully disabling inflammatory process. Both can be accomplished by excision of a two-inch segment of the main saphenous vein at its junction with the femoral vein and ligation of the divided ends. Rather dramatic relief of pain and rapid subsidence of the inflammatory process occur following division of the venous trunk, a fact substantiated by Welch and Faxon,¹² Fine, Frank, and Starr,¹³ and Heyerdale and his co-workers.¹⁴ The mechanism of pain relief is thought to be due to interruption of the sympathetic fibers which pass alongside of the vein, lying in its tunica adventitia. This explanation is based upon the frequently observed abolition of pain in deep femoral thrombophlebitis after procaine block of the lumbar sympathetic ganglia. Actually, sympathetic ganglion block is a rational form of treatment of saphenous thrombophlebitis inasmuch as it accomplishes both relief of pain and subsidence of the inflammatory process. It does not, however, offer full protection against proximal propagation of the thrombus and possible embolism. For this reason, excision and ligation constitute a preferable method of treatment when the deep circulation has been found to be patent by clinical and venographic studies.

When excision-ligation has been chosen as the method of treatment of acute saphenous thrombophlebitis, the question arises as to the need for simultaneous retrograde sclerosing injection. In the presence of involvement of the entire great saphenous trunk by the phlebitis, additional inflammatory activity of a chemical sort should be avoided. As the original phlebitis subsides following ligation and division, an extensive degree of obliteration of the venous channel results from fibrosis. When, however, only a portion of the vein is affected by the phlebitis, sclerosing injection of the uninvolved segment should be done at the

time of ligation and division. More than one incision may be necessary to isolate the uninvolved segment for catheterization, as occurs when only that portion of vein from the saphenofemoral junction to the knee is the site of an inflammatory obstruction. Cases 4 and 5 illustrate two variations encountered in managing superficial thrombophlebitis.

CASE 4 (Roper Hospital No. 24127).—A 44-year-old Negro woman entered the hospital Nov. 17, 1943, complaining of tenderness, pain, and swelling of the left leg. One week previously the patient suffered from chills and fever, during which time a small ulcerative lesion appeared above the lateral malleolus of the left ankle after a slight injury to that region. On examination, the entire great saphenous vein was found to be indurated, hot, and tender to manipulation. Inguinal lymph node enlargement was present. The patient was afebrile. Division of the saphenous trunk was done at the fossa ovalis and ligation of the divided ends was accomplished without retrograde injection. Twenty-four hours after operation there was complete disappearance of both subjective and objective discomfort and the phlebitis had subsided satisfactorily. The patient was discharged forty-eight hours after operation with complete subsidence of the phlebitis and entirely free of pain. Follow-up observations in the outpatient department found her free of demonstrable varicosities. The small ulcer noted on admission healed within a week.

CASE 5 (Roper Hospital No. 23983).—A 59-year-old white woman was admitted Nov. 15, 1943, because of a diffuse cellulitis of the lower half of her left leg, extending over the proximal portion of the dorsum of the foot. There was present, also, a well-defined acute thrombophlebitis of the great saphenous vein from ankle to knee. The vein was hot and extremely tender and was palpable as a thickened indurated cord. There was no involvement within the thigh. The patient had no history indicating the source of her infection and no portal of entry was discovered on physical examination. In view of the rather virulent nature of the cellulitis, it was decided to defer ligation-division of the saphenous vein. Accordingly, novocaine infiltration of the left lumbar sympathetic ganglia was done shortly after admission. One hour later she stated that she was "considerably relieved" of pain. Seven hours later there was evidence that the cellulitis was subsiding and at the end of twenty-four hours it had been reduced to 50 per cent of its original extent. The sympathetic block was repeated after thirty-six hours and was followed by complete disappearance of the cellulitis. Three days after admission, the saphenous vein was barely palpable below the knee, practically all induration having subsided. At this time operative treatment was carried out as follows: the main saphenous trunk was exposed just above the knee and ligation-division completed, thus isolating the lower segment previously involved by the phlebitis; retrograde injection was not done. Exposure of the saphenofemoral junction was then accomplished and ligation-division again carried out. In this manner, the thigh segment of vein, which had not been affected by the phlebitis, was isolated and subjected to catheterization and segmental injection of sclerosing material. Convalescence was uneventful and the patient is now considered to be free of demonstrable varicose veins.

Lymphangiitis and Cellulitis.—Diffuse reticular lymphangiitis, manifested by marked hyperemia, brawny induration, increased local heat, tenderness, and pitting edema of the involved area, is seen rather often in the lower half of the leg in the presence of venous stasis. Frequently no bacterial portal of entry can be demonstrated or a small ulcer may be an associated finding. Acute superficial thrombophlebitis

sometimes precedes and accompanies the process. In either case, procaine infiltration of the ipsilateral lumbar sympathetic ganglia is of great benefit and is followed by rapid resolution of the inflammatory process. Case 5 is a typical example of favorable response to sympathetic block. The following case represents a diffuse inflammatory process of different etiology, successfully treated by paravertebral novocaine infiltration.

CASE 6 (Roper Hospital No. 17575).—A 58-year-old white man was admitted Feb. 7, 1944, because of bilateral varicose veins. A scaly varicose eczema was present over the right ankle and lower leg and showed several weeping areas of superficial denudation. After three days of preliminary treatment of the eczema by warm moist dressings, bilateral saphenous ligation and retrograde injection were performed; catheters were passed 60 cm. down each vein and 10 c.c. of 5 per cent sodium morrhuate solution were injected segmentally into each vein. The resulting chemical thrombophlebitis was marked and considered satisfactory. On the second postoperative day the patient presented evidence of an extensive spreading cellulitis from ankle to knee of the right leg and complained of much pain in the area. The temperature was elevated to 102° F. A right paravertebral novocaine infiltration was done at the levels of the first through the fourth lumbar vertebrae. Within twenty-four hours, the entire inflammatory reaction had subsided and the patient was free of discomfort. Follow-up studies in the outpatient department showed healing of the dermatitis to be slow but finally complete. The varicose veins were considered cured.

Varicose Ulcer.—The underlying factor in the causation and perpetuation of varicose ulcer is chronic tissue hypoxia incident to venous stasis. When of long duration, hypoxia results in tissue fibrosis. The presence of fibrosis about an ulcer renders the latter extremely resistant to cure, even after successful elimination of venous stasis, because of the pronounced diminution in vascularity of the fibrous tissue. This factor can be combated to a large extent by interruption of the sympathetic impulses of the affected extremity.

In cases of long-standing, indolent, varicose ulcer, combined sympathectomy and saphenous ligation-division are recommended. The rationale of combining these procedures is based upon two factors resulting from the vasodilatation produced by sympathectomy: (1) tissue oxygen tension is rapidly increased and sustained, and (2) increase in phagocytosis and collateral circulation is accomplished. The first factor is self-evident while the second has been demonstrated in experimental observations of "local shock" by Thomson, Helwig, and Sire.¹⁵ The increase in vascularity of the extremity, when combined with obliteration of the varicose veins, aids materially in healing the indolent types of ulcer.

Technically, sympathectomy can be performed in one of two ways in the lower extremity. Either lumbar ganglionectomy or femoral periarterial sympathectomy will eliminate impulses of sympathetic nervous origin in the legs. A third method, crushing the mixed peripheral nerves, is hardly applicable to leg ulcers because of the exten-

sive loss of motor function incurred by the operation. Periarterial sympathectomy produces only temporary vasodilatation, regeneration occurring within a few weeks. However, its effects seem to be of sufficient duration to augment the elimination of tissue hypoxia and, when combined with the operative cure of varicose veins, to permit healing of the ulcer to begin. Once venous stasis has been abolished the healing process progresses usually to complete cure. In the event of recurrence of the ulcer, the more formidable operation of lumbar ganglionectomy deserves consideration.

CASE 7 (Roper Hospital No. 22886).—A 41-year-old white man entered the hospital Oct. 9, 1943, because of left saphenous varicosities and severe varicose eczema. The lower half of the left leg was red, indurated, and leathery and showed a superimposed scaling ulcerative dermatitis. Marked fibrosis was present and, with the patient standing, a suffused cyanotic appearance of the leg developed, indicating advanced venous stasis and tissue hypoxia. After twelve days of preliminary treatment of the dermatitis, combined femoral periarterial sympathectomy and saphenous ligation-division and injection were performed through a vertical incision (Fig. 4) in Scarpa's triangle. A ureteral catheter was passed distally 20 cm. from the fossa ovalis, and 10 c.c. of 5 per cent sodium morrhuate solution were injected as the catheter was withdrawn upward. The main saphenous vein was exposed again just above the medial condyle of the femur and catheterization-injection distally was repeated. The patient developed a very satisfactory chemical thrombophlebitis and the skin temperature of the toes became greater than that of the unaffected extremity. Prompt healing of the ulcerations and dermatitis and disappearance of the varicose veins resulted.

Severe Postoperative Vasospasm.—Generalized spasm of the arterioles and small veins of an extremity is initiated by an inflammatory process within one of the main venous trunks. Experimentally, DeBakey, Burch, and Ochsner¹⁶ have shown that a chemical endophlebitis, localized to a given segment of a large vein, causes vasospasm of sufficient severity to reduce greatly the volume of peripheral pulsations in the affected limb. They have demonstrated also that the responsible vasoconstrictor impulses, originating in the phlebotic segment, can be abolished by sympathectomy or by novocaine ganglion block, resulting in restoration of the peripheral pulsations to normal.

From a practical standpoint, the clinical counterpart of this phenomenon should be encountered often in the treatment of varicose veins where large amounts of sodium morrhuate are used. Actually, it is rare, but it does occur and may be of alarming degree, as illustrated by the following case.

CASE 8 (Roper Hospital No. 118745).—A 53-year-old white man was operated upon Aug. 15, 1941, for extensive varicose veins of the left leg. The main saphenous vein was exposed at the fossa ovalis and just above the knee. The distal segments and several tributaries at each site of exposure were catheterized and injected with a total of 28 c.c. of sodium morrhuate, 5 per cent aqueous solution. Shortly after the patient's return from the operating room, the lower third of the leg and the entire foot became cyanotic and cold, and sensation in the involved area was impaired. The dorsalis pedis artery was palpable. Normal color was

restored by next day after keeping the entire left leg in a heat cradle for several hours. Sympathetic novocaine block was not done but it is now believed that the changes observed in the affected limb were those of severe vasospasm incident to the associated chemical phlebitis.

EDEMA

The presence of edema may complicate the general management of the patient with varicose veins during both the preoperative and postoperative periods. As a preoperative accompaniment of varicosities, edema is a complicating factor mainly from a diagnostic standpoint. It may be of sufficient degree to mask the presence of varicose veins; it may cause a misinterpretation of tourniquet tests by interfering with emptying of distended superficial veins; and it may be due to deep venous obstruction, in which event the presence of varicosities would be the result of processes producing the edema rather than the cause. Under these circumstances, it seems clear that preoperative evaluation of the patient having both varicose veins and edema is incomplete without venographic study of the affected extremity. The routine employment of phlebography under the conditions noted clarifies the circulatory status of the edematous limb and affords a safeguard against saphenous ligation in the presence of femoral venous insufficiency.

The postoperative occurrence of edema in the leg which showed only varicosities before operation constitutes a complication of considerable magnitude. In the presence of partial obstruction or impairment of function of the deep venous system, the sudden obliteration of the saphenous tree by ligation-division and sclerosis results in curtailment of venous return of sufficient degree to cause edema. Although preoperative tourniquet tests are extremely helpful, they are not specific enough to demonstrate subclinical degrees of diminished venous return in the deep circulation. Since such impairment occurs chiefly in women past middle life who have had multiple pregnancies, careful preoperative study of this class of patients is essential and should include venography. Once postoperative edema becomes established, it persists until recanalization of the deep system has occurred. Increase in collateral circulation and promotion of recanalization can be effected by repeated novocaine injections of the lumbar sympathetic ganglia. This form of treatment is recommended as of considerable value, as evidenced by the following case.

CASE 9 (Roper Hospital No. 19046).—A 45-year-old white housewife received the usual ligation-division and sclerosis treatment for bilateral varicose veins in May, 1943. A good sclerosis was obtained and the varicosities rapidly disappeared. However, progressively, increasing edema of the right leg developed after operation and could be controlled only by bed rest. In August, 1943, two paravertebral sympathetic ganglion blocks with novocaine were done twenty-four hours apart. Edema subsided quickly and recurred only to a slight degree after several days of activity. It gradually decreased in extent and finally disappeared completely after one month.

PERSISTENCE OF VARICOSITIES AFTER OPERATION

As previously stated, the objective in the treatment of varicose veins is as nearly complete obliteration of the saphenous tree as possible. If the ligation-division and injection technique is employed, this can be accomplished only by extensive sclerosis which results from the use of large quantities of sclerosant introduced by ureteral catheter in a segmental manner. The chemical thrombophlebitis which follows injection of 20 c.c. or more of 5 per cent aqueous solution of sodium morrhuate is widespread to the extent of being incapacitating. For this reason, hospitalization is advised until the patient's discomfort has diminished. It is believed that the average patient is more willing to submit to a few days of hospitalization than to ambulatory operative methods involving many office injections after operation. Massive sclerosis can be accomplished only by segmental catheter injection and should be done only in hospitalized patients. It represents the principal means of materially reducing the number of follow-up office injections which are both time consuming and disagreeable to the patient.

The majority of patients with varicose veins need no more than one or two postoperative sclerosing injections, so thorough is the obliteration obtained by the massive sclerosis method. A few, however, will show persistence of several veins which must be dealt with one at a time. This is true of individuals having unusual degrees of tortuosity or other anatomic variations which interfere with catheterization at operation. In order to minimize the number of postoperative visits and obtain a maximum degree of sclerosis, injection should be done at the lowest level possible with the extremity elevated, as advocated by Bellis and Churney.¹⁷ It was pointed out earlier in this discussion that sclerosing agents tend to become fixed very rapidly, especially in the presence of a static column of blood. By elevating the leg, the veins are emptied and the sclerosant is allowed to diffuse over a greater surface of intima and thus produce more extensive thrombosis.

REACTIONS TO SCLEROSING AGENTS

While the ligation-injection treatment of varicose veins has been established as a safe and effective method of therapy, undesirable reactions occasionally follow the use of certain sclerosing agents, notably sodium morrhuate. Anaphylactoid responses of extremely severe character have been reported in a few instances after the use of the latter drug.¹⁸⁻²¹ Although the mechanism of the reaction is obscure, it seems clear that it is prone to occur upon the resumption of injection treatment in patients who have remained untreated for several months after an initial course of sclerosing therapy, suggesting a sensitization phenomenon. As noted by Prioleau,²² a minor reaction or a lapse of time between injections should serve as a warning to adopt a different sclerosing agent if further injection treatment is necessary. By em-

ploying the massive sclerosis method of ligation-division and catheterization at the outset, very few follow-up injections are necessary and the dangerous time interval between treatments can be eliminated.

Severe manifestations of an unfavorable reaction to sodium morrhuate are essentially anaphylactic in nature, consisting of angioneurotic edema, asthmatic dyspnea, and peripheral circulatory collapse. I have not encountered such a response during several years of routine use of sodium morrhuate in a representative number of patients. Two toxic reactions have occurred, however, one of a mild and transient nature, the other an extremely severe systemic response of unusual character.

CASE 10 (Roper Hospital No. 20175).—A 26-year-old white man was subjected to bilateral saphenous ligation-division, multiple venous catheterizations, and massive sclerosis with sodium morrhuate in June, 1943. A total of 50 c.c. of the sclerosant was injected through the catheters in the two legs. On the second postoperative day, 5 c.c. of sodium morrhuate were injected into the right main saphenous vein at the ankle and on the seventh postoperative day, 4 c.c. were injected into a varix below the right knee. The left leg did not require further injections. The postoperative course was uneventful and the patient left the hospital showing a satisfactory degree of thrombosis.

One month later, examination revealed complete disappearance of all varicosities except for a small patch in the region of the right knee. Accordingly, 5 c.c. of sodium morrhuate were injected into the remaining veins with the leg elevated. Thirty minutes after the injection, the patient developed a mild headache which was accompanied by hemianopsia. Within two hours, the reaction had reached the peak of its intensity and consisted of severe headache, hemianopsia, and vertigo. The visual disturbance was transient, disappearing and recurring at intervals. The entire syndrome subsided within five hours, leaving no ill effects.

*CASE 11 (Roper Hospital No. 33958).—A 66-year-old white farmer entered the hospital in November, 1944, presenting extensive varicose veins of both legs. Examination revealed an unusually severe degree of varicosity of each saphenous system, sacculation and pooling being marked in both thighs as well as in both legs. Scars of previous ulceration were noted about the ankles but no active ulcers were present. Trendelenburg and Perthes tests were positive and there was no past history suggestive of deep venous obstruction. The patient's blood pressure was 155/100. Total white blood count was 5,950 with normal differential picture; red blood count, 4,295,000; hemoglobin, 12 Gm. The urinalysis was normal and the blood urea nitrogen level was 11 mg. per cent.

Because of the widespread extent of the varicosities, two operative procedures were done three days apart. The left leg was treated first in the routine manner by multiple ligations, catheterizations, and injections. The main saphenous vein and its principal tributaries were exposed through five separate incisions, and a total of 25 c.c. of sodium morrhuate was injected through the catheters. No untoward reaction occurred. The immediate postoperative course was satisfactory and the resultant widespread chemical thrombophlebitis was considered adequate.

Operative treatment of the right leg was done after an interval of three days. Because of the remarkable nature of the patient's reaction, the procedure is described in some detail. Local infiltration anesthesia of 1 per cent novocaine was used. Through a transverse incision over the fossa ovalis (Fig. 3), the saphenofemoral junction was exposed. Four tributaries of the great saphenous vein were

ligated and divided; none was injected. The saphenous vein itself was then divided close to the femoral junction and its proximal stump was ligated and transfixed. A two-inch portion of the vein was excised and the distal segment was then catheterized with a No. 5 ureteral catheter. The latter was passed downward a distance of 25 cm. without obstruction, but could not be palpated anywhere in the subcutaneous tissues of either the thigh or leg. Because of failure to demonstrate the catheter within the superficial venous system, it was withdrawn without injection and the wound was packed open temporarily with saline sponges. A large plexus of veins occupying the entire anterior surface of the leg was next isolated between incisions at the ankle and in the upper portion of the calf. Catheterization and injection were done, using 7 c.c. of sodium morrhuate, and the wounds were sutured. There was no reaction. The next step was re-exposure of the great saphenous vein just above the knee (Fig. 3). After dividing the vessel, the usual procedure was reversed and the catheter was passed upward toward the groin. Although no obstruction was encountered, the catheter failed to appear at the groin wound and still could not be palpated in the subcutaneous tissues of the thigh. It was withdrawn again without injection and the divided ends of the vessel were ligated. After closure of the supracondylar incision, a final attempt was made to catheterize the great saphenous vein from above. Its downward passage was unobstructed but it could not be palpated through the skin. Despite failure to demonstrate the location of the catheter by palpation, injection of sodium morrhuate was undertaken. When the catheter had been passed 20 cm. from the fossa ovalis, it was withdrawn slowly upward as 5 c.c. of sodium morrhuate were injected through it. Immediately upon completion of the injection, a severe systemic reaction occurred. The patient screamed out because of intense pain located in the midline of the lumbar area of his back. The discomfort developed suddenly and remained confined to its original location without radiation. A hard, shaking chill developed and increased the intensity of the back pain. One-sixth grain of morphine sulfate was given subcutaneously. The patient was removed from the operating table within twelve minutes of the onset of the backache, at which time his pulse was 160 and blood pressure 160/120. Upon reaching his room, he showed signs of mental confusion and the blood pressure fell to 100/70. Within twenty minutes of the onset, the patient was completely disoriented, although conscious, and his blood pressure was 70/40. At this time, 750 c.c. of 5 per cent glucose in normal saline solution were given intravenously, followed by a transfusion of 500 c.c. of whole blood. Within three hours of the onset, the blood pressure was 100/70, but the patient remained confused and disoriented. The axillary temperature was 103° F. Seven hours after the onset, the blood pressure again fell precipitously to 70/50 and the pulse became weak, rapid, and thready. There was still no loss of consciousness and 500 c.c. of plasma were given intravenously; the blood pressure gradually returned to a satisfactory level and was sustained thereafter around 110/75. After ten hours, the patient was mentally clear and his backache had subsided.

During the twenty-four hours after the onset of the reaction, the urinary output was only 210 c.c., while the combined intravenous and oral intake of fluid was 2,330 c.c. The oliguria was transient and a satisfactory output established on the first postoperative day was maintained thereafter. Despite this, the blood urea nitrogen level reached 55 mg. per cent, creatinine 3.82 mg. per cent on the second postoperative day, and returned to normal only after ten days. Repeated urinalyses showed low specific gravity, 2 plus albumin, 2 to 4 pus cells, 1 to 3 red blood cells, and numerous coarse granular casts per high-power field.

The patient was discharged from the hospital sixteen days after the second operation. At that time, it was thought that an excellent result had been obtained, only a few scattered varicose veins remaining. There were apparently no serious consequences of the reaction.

Comment.—The reaction noted in Case 11 was, in all probability, not due to hypersensitivity to sodium morrhuate. This is probably true for three reasons. First, the time interval between injections was only three days; second, injection of several veins below the knee was carried out prior to the thigh injection without a reaction; third, the clinical manifestations were not those of an allergic reaction, that is, there was no urticaria, asthmatic dyspnea, or mucous membrane exudation. The general systemic response was undoubtedly initiated by the injection of the sodium morrhuate into the general circulation by way of the femoral vein. Inasmuch as the catheter could not be palpated in the subcutaneous tissues, one can assume that it had entered the femoral vein through a large communicating vessel. This is especially likely in view of the free, unobstructed progress of the catheter as it was passed along the vein. The fact that there was no subsequent evidence of femoral obstruction (due to sclerosis) does not mitigate the latter possibility, because sclerosis from sodium morrhuate occurs only in the presence of venous stasis. If the foregoing reasoning is correct, the reaction can be considered as a specific response of the general organism to a large amount of sodium morrhuate delivered directly into the systemic circulation.

SUMMARY

1. Radical surgical treatment of varicose veins by high ligation-division, catheterization, and massive segmental sclerosis is recommended as the method of choice in obtaining a large percentage of satisfactory results.

2. Factors which tend to complicate the treatment of varicose veins are discussed and illustrative case reports are presented under the headings of anatomic variations, thrombophlebitis, cellulitis, ulcer, postoperative vasospasm, edema, persistence of varicosities after operation, and reactions to sclerosing agents.

3. The interruption of sympathetic nerve impulses as an adjunct in managing certain complications is discussed.

4. A case report of an unusually severe reaction to sodium morrhuate is presented in detail.

REFERENCES

1. Pratt, G. H.: Segmental Sclerosis of the Saphenous Vein for Varicose Veins, Ulcers and Diminished Arterial Supply, *J. A. M. A.* 113: 925, 1939.
2. Pratt, G. H.: Results of Surgical Treatment of Varicose Veins, *J. A. M. A.* 122: 797, 1943.
3. Ochsner, A., and Mahorner, H.: *Varicose Veins*, St. Louis, 1939, The C. V. Mosby Company.
4. Smithy, H. G.: The Surgical Management of Varicose Veins and Ulcers, *J. South Carolina M. A.* 36: 307, 1940.
5. Adams, R.: The Treatment of Varicose Veins and Varicose Ulcers, *S. Clin. North America* 22: 933, 1942.
6. Heyerdale, W. W., and Stalker, L. K.: Management of Varicose Veins of the Lower Extremities, *Ann. Surg.* 114: 1042, 1941.
7. Pearce, M. B.: Varicose Veins, *SURGERY* 14: 901, 1943.

8. Stalker, L. K., and Heyerdale, W. W.: The Technique of Combined Division, Ligation, and Injection of the Incompetent Great Saphenous Vein, *Surg., Gynec. & Obst.* 70: 1094, 1940.
9. Sarma, P. J.: The Treatment of Varicosity of Lower Extremities, *South. Surgeon* 11: 514, 1942.
10. Grimson, K. S.: Personal Communication.
11. Ochsner, A., and DeBakey, M.: Thrombophlebitis: The Role of Vasospasm in the Production of the Clinical Manifestations, *J. A. M. A.* 114: 117, 1940.
12. Welch, C. E., and Faxon, H. H.: Thrombophlebitis and Pulmonary Embolism, *J. A. M. A.* 117: 1502, 1941.
13. Fine, J., Frank, H. A., and Starr, A.: Recent Experiences With Thrombophlebitis of the Lower Extremity and Pulmonary Embolism, *Ann. Surg.* 116: 574, 1942.
14. Heyerdale, W. W., Clagett, O. T., and Anderson, E. M.: The Treatment of Acute Superficial Thrombophlebitis in an Incompetent Venous System of the Lower Extremities, *Proc. Staff Meet., Mayo Clin.* 18: 1, 1943.
15. Thomson, J. E. M., Helwig, F., and Sire, E.: Sympathetic Block in the Treatment of Local Shock, *J. Bone & Joint Surg.* 26: 189, 1944.
16. DeBakey, M., Burch, G. E., and Ochsner, A.: Effect of Chemical Irritation of Venous Segment on Peripheral Pulse Volumes, *Proc. Soc. Exper. Biol. & Med.* 41: 585, 1939.
17. Bellis, C. J., and Churney, O. L.: Injection of Varicose Veins, *SURGERY* 13: 411, 1943.
18. Zimmerman, L. M.: Allergic-Like Reactions From Sodium Morrhuate, *J. A. M. A.* 102: 1216, 1934.
19. Lewis, K. M.: Anaphylaxis Due to Sodium Morrhuate, *J. A. M. A.* 107: 1298, 1936.
20. Hatcher, M. B., and Long, H. W.: Unfavorable Reactions From Sodium Morrhuate, *J. M. A. Georgia* 26: 427, 1937.
21. Dobson, L.: Sodium Morrhuate Reactions, *Ann. Surg.* 111: 645, 1940.
22. Prioleau, W. H.: Complications Connected With the Treatment of Varicose Veins in the Leg, *J. South Carolina M. A.* 37: 204, 1941.

CLINICAL ANATOMY OF THE VERTEBRAL VEINS

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THE various explanations offered for the spread of so-called "paradoxical metastasis" have, until recently, been unsatisfactory. Fig. 1 illustrates such a case and shows metastasis to the cervical spine from carcinoma of the prostate, without x-ray evidence of metastasis to the lung. How do such metastases reach the cervical vertebra through the usually accepted avenues of spread? Likewise, metastasis to the spine can be found in early carcinoma of the breast without evidence of lymph node metastasis. The frequency with which suppurative or malignant processes in the thorax produce intracranial lesions is such as to point to anatomic structures conveying these organisms or cells to the cranium.

Everyone is familiar with the usual mode of spread of infection or malignancy. The first is by lymphatics, where the organism or tumor cell migrates into the lymphatic channels and is transported to the adjacent lymph nodes where it is filtered out. Eventually, if the bacteria or tumor cells reach the thoracic duct, they will finally enter the venous circulation which leads directly to the right side of the heart and then to the lungs. That such an organism or cell can filter through the tissues of the lung, without setting up a local focus in the lungs, is highly improbable. Therefore, one would expect to find definite evidence of metastasis to the lungs before finding metastasis to other parts of the body, such as the spine.

The second mode of distribution of bacteria or tumor cells is by way of the veins. In this case, bacteria or tumor cells infiltrate into venous channels by erosion of the original lesion into such channels. In such instances, the spread would be along the same route, namely, into the caval system to the right heart and to the lungs.

Finally, spread of the disease is sometimes carried by the arterial system directly. In such cases, the bacteria or cells enter the arterial system by erosion of the original lesion into the pulmonary veins, then to the left side of the heart to the systemic arterial circulation. A typical example of this is miliary tuberculosis.

To explain the so-called "paradoxical metastasis" different theories, supported in some instances by careful work, have been advanced. One is that in some patients there is a patent foramen ovale, and that the bacteria or tumor cell finds its way to the left side of the heart through the foramen ovale and is then spread by the arterial system. In such event, the lodging of the cell or embolus would be purely accidental. This theory is traced to the two cases published by Litten,¹ 1880, and Cohnheim,² 1889, in which the foramen ovale was patent. Since then,

Received for publication, Dec. 28, 1944.

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this theory has been copied in textbooks of pathology, and credence has been given to this theory, although Cohnheim stated that, "the locality to which the detached thrombi are transported is determined by anatomical conditions alone."

Another theory is that advocated by Warren, Harris, and Graves³ who state: "While hematogenous metastasis may occur in carcinoma of the prostate, the chief factors in the marked preponderance of metastatic lesions in the pelvis and in the lower regions of the spine are the distribution of the nerves and the condition of the tumor cells along the perineural lymphatic spaces, and the close contact with the bone." The perineural lymphatic dissemination of the tumor may be either by continuity or through embolism. No doubt local metastasis occurs in this manner at times. But these authors do not attempt to explain distant metastasis of the prostate such as shown in Fig. 1.



Fig. 14.—Showing extensive metastasis to the cervical vertebra from carcinoma of the prostate.

A different explanation offered is that tumor cells have affinity for certain tissues; thus, carcinoma of the prostate is said to have predilection for metastasis to bone and carcinoma of the lung selects brain tissue when it is separated from its mother lesion.

Finally, one theory is based upon careful histologic studies of the lungs, where it has been found that tumor cells were present in the lungs without having produced sufficiently large metastasis to be detected by x-ray. This has been found in cases where obvious distant metastasis have been demonstrated. It has been proposed that the

tumor cells have been transported into the lungs and thence into the left side of the heart without producing growth in the lungs. The objection to this is that it is highly improbable, as lung tissue is a fertile field for the growth of both bacteria and tumor cells. As Batson has pointed out, these findings could be explained more readily as terminal events and as having come from the secondary metastasis.

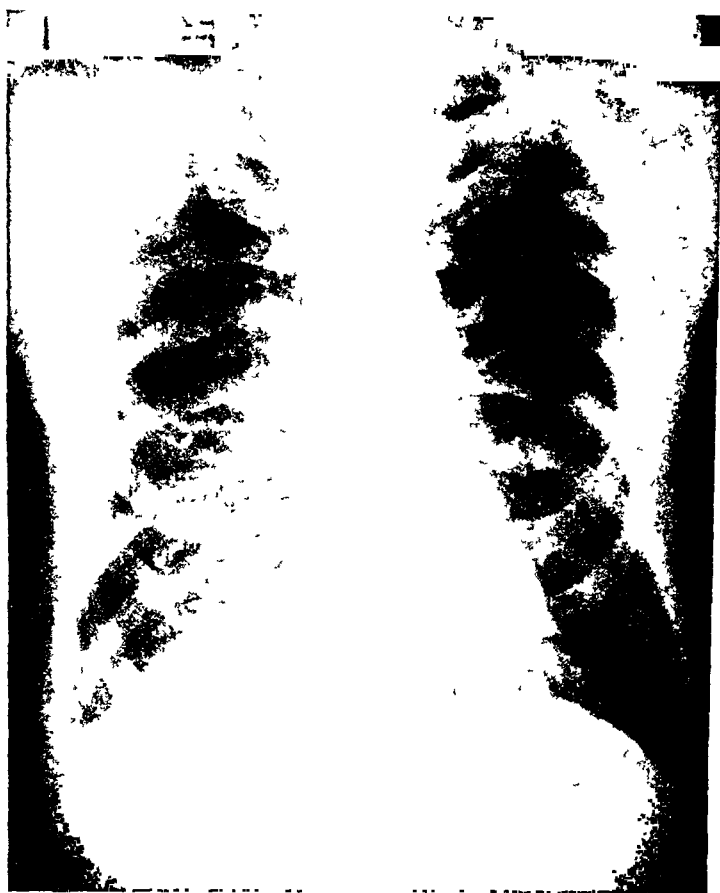


Fig. 1B.—Showing no x-ray evidence of metastasis to the lungs. Same case as Fig. 1A.

In 1940, Batson⁴ published his report on the rediscovery of the vertebral system of veins. While it is true, as Harris⁷ has pointed out, that the vertebral system of veins was described and understood over 100 years ago, credit should be given Batson for rediscovering this system of veins, employing the injection method. Standard textbooks of anatomy and even Franklin's⁸ *A Monograph on Veins*, 1937, make no mention of this system. Forgotten knowledge is equivalent to no knowledge. Batson's approach is entirely new and demonstrates more clearly the connections between this and other venous systems than could be done by dissection.

In reviewing the history of the early work on the vertebral system of veins, I have drawn freely on the article by Harris.⁷ The early anatomists were familiar with the spinal veins and their connections. Bock⁹ of Leipzig, in 1823, published a work called *Darstellung der Venen* in which he demonstrated most completely the rich venous plexuses of the inside of the bony spinal canal with dominance of the longitudinal anastomoses between the bony canal and the theca of the dura mater. Bock also pointed out that the sacral branches of the internal iliac veins communicate freely with the veins within the spinal canal through the anterior spinal foramina. The posterior plexus on the back of the sacrum does the same through the posterior sacral foramina. All the communications with the cranial venous sinuses are given in detail. He pictures the transverse anastomosis between the two longitudinal channels and describes a "circellus venosus" which is situated on the posterior aspect of the body of each vertebra. These receive tributaries from the marrow cavity of the vertebra. Willis¹⁰ in 1664, Winslow¹¹ in 1732, Breschet¹² in 1832, and Cruveilhier¹³ in 1834, all knew about the spinal veins.

SUMMARY OF BATSON'S WORK

In his first experiment, Batson injected the dorsal vein of the penis with a fairly thick solution of King's yellow artist's water color, and found that the material entered the smaller veins of the pelvis along the prostate, thence to the iliac vein, and into the vena cava. When a thin solution of Weber's artist's water color vermilion was used, the material went into the veins of the ileum, then it progressed to the spine. Some of the intercostal veins were filled, and after he had injected a total of 200 c.c., the material was found at the base of the skull and in the cranial cavity. The substance also went distally to the vessels of the right thigh where it was found that these vessels were the vena vasorum of the femoral vessels. None of the material entered the vena cava. He then injected the dorsal vein of the penis of the macacus rhesus monkey with colloidal thorium dioxide. The material was found to go into the pelvic veins and ascend to the inferior vena cava. When pressure was made on the inferior vena cava, the material entered the vertebral system of veins as well as the vena cava.

When the small veins of the female breast were injected with this solution, it was found that it spread to the clavicles, to the intercostal veins, to the head of the humerus, to the cervical vertebra, and to the transverse and superior longitudinal sinuses of the skull. It also entered the azygos vein and the superior caval system. He then injected the small veins adjacent to the nipple and found that the material spread to the tissues immediately adjacent to the point of injection, and sometimes to the opposite breast as well as more distally to the scapula and humerus.

Batson's report offered an anatomic explanation for "paradoxical metastasis." Because of its great interest and practical importance, the experiments have been repeated. The dorsal vein of the penis was injected with Weber's artist's water color vermilion. By taking serial x-rays of the body, it was demonstrated that the injected mass flowed through veins along the pelvic girdle as far distant as the head of the femur, along the vertebral column, and finally inside the cranium, without entering the vena cava. Five cadavers were used, and in four the flow was as described; in only one the material entered the vena cava and did not proceed up the vertebral column. Unfortunately, due to lack of suitable material, I was unable to repeat his work on the injection of the female breast.



Fig. 2A.—Showing cannula in dorsal vein of penis. The material is shown ascending into the vertebral veins.

DISCUSSION

Once a carcinoma cell or bacterial embolus has been ushered into the vertebral system of veins, how can it reach distal structures against the usual direction of flow of blood? Thus, how does cancer of the breast produce metastasis to the lumbar vertebra or to the proximal end of the femur if the tumor cell would have to flow "upstream" as it were? Likewise, how does a bronchogenic carcinoma cell reach the vertebral system,

and from there, how is it transported inside the cranium against the normal flow of venous blood? Batson⁴⁻⁶ states that reversal of flow in the vertebral system of veins does occur under certain circumstances such as sneezing, coughing, or straining. Thus, when a person is in the upright position, anything that increases the pressure within the body cavities would predispose to reversal of flow, with gravity. Likewise, when in the prone position, reversal of flow to the head would be facilitated. Batson also found that the pressure in the vertebral system of veins is low, considerably lower than in the caval system. Also, the spinal veins have no valves, a factor which is of great importance in the reversal of flow. On this subject, John Hilton,¹¹ 1855, stated: "The



Fig 2B.—Showing the material ascending in the dorsal and cervical region without being present in the inferior vena cava.

absence of valves in the whole of these venous tubes is a circumstance which is doubtless connected with a wise intention. It enables the blood to pass in either direction, and consequently, greatly increases the freedom of venous circulation, a point of essential importance with an organ whose functional capacity is so liable to interruption under so slight a disturbance of the balance of its circulating fluid."

What further evidence is there to support reversal of flow of fluids in the body? According to Franklin's⁸ monograph on veins, the summary

of the findings of different workers measuring venous pressures shows generally that the pressure in the more distant veins is higher, up to plus 11 or 12 mm. of mercury, and as the venous blood approaches the superior vena cava, it may be minus 2.8 mm. of mercury. It is also minus in the external jugular vein. According to the same author, Ledderhose,⁸ in 1906, pointed out that there can be a backward wave of blood in veins without backward movement of blood. Retrograde movement of blood is said to occur at the site of the venous valves. Naegeli



Fig. 2C.—Showing material in the vertebral veins of the cervical region entering the cranium.

and Janker⁸ performed experiments on embolism. Under x-ray, emboli were injected into the femoral vein, passed up the abdominal vena cava, stayed for a while near the diaphragm, and then shot along the thoracic inferior vena cava to the right auricle. Thereafter they often came back again to the diaphragm before going through the heart. Franklin⁸ states: "Under pathological conditions of the venous system in man, change of posture must at times result in temporary reversal of flow in veins." Other workers have noted backward flow of blood in the veins. Certain evidence of backward flow of fluids in the body is pres-

ented by Hamilton, Woodbury, and Harper.¹⁵ These workers experimented with a monometer of their own construction, measuring the effect in the arterial system of sneezing, coughing and straining. There was definite, and at times, rather marked increase in the systolic and diastolic pressures, sometimes up to 100 mm. of mercury. They also measured the intraspinal pressure and found it to rise markedly during coughing and sneezing. No measure was made of the venous pressure. But it can be inferred from the experiments that there is also a rise in the venous pressures.

Now, as to the pathways through which a bronchogenic carcinoma cell can be transported into the vertebral system and thence to the cranial cavity, Lee,¹⁶ in 1922, performed experiments ligating the thoracic duct. His summary is as follows: "It seems that the integrity of the thoracic duct is not essential to the life of the animal. In some cases in which the ligation was absolute, collateral lymph circulation was established to the right thoracic duct; while in other cases which showed complete ligation, *lymphaticovenous connections were found to exist between the thoracic duct and the azygos vein.*" Batson demonstrated connection between the azygos and vertebral system of veins.

It is quite conceivable that metastatic bronchogenic carcinoma cells can be transported into the vertebral system, either through the lymphatics of the lung emptying into the lymphatic system, or by retrograde flow into the azygos system, and thence into the vertebral system. It is also possible that such cells might enter bronchial veins, thence into the azygos veins and into the vertebral system.

Clinical application of the vertebral system of veins as channels, through which infected emboli are transported, has been made by Martin.¹⁷ He reports three cases of superior sinus thrombosis following childbirth, with one fatality.

From the forgoing experiments, one is justified in concluding, that there is reversal of flow, not only in the vertebral system of veins, but also in other veins as well as the lymphatic channels.

THE VERTEBRAL VEINS—A DETOUR FOR BLOOD

Recent work on ligation of large venous channels for thrombosis and embolism, such as the femoral, iliac, or even the inferior vena cava itself, has re-emphasized the part that the vertebral system of veins play in returning blood from the lower extremities. This also, according to Harris, was known over 100 years ago. Cruveilhier,¹⁸ 1834, wrote: "The veins of the spine are such that one may consider them, in relation to the general circulation, as establishing an uninterrupted communication between the veins of all parts of the trunk: so that one may conceive either of the two venae cavae to be obliterated, without interruption of the venous circulation. Even the vena azygos major, usually considered as the main route of communication between the superior and inferior

vena cava, is not necessary, in view of the presence of the anterior and posterior rachidian plexus. This explains why I have seen at one time the inferior vena cava, at another the superior vena cava obliterated without any visible enlargement in the calibre of the azygos vein, and which may seem surprising, without any edema either of the upper or lower limbs."

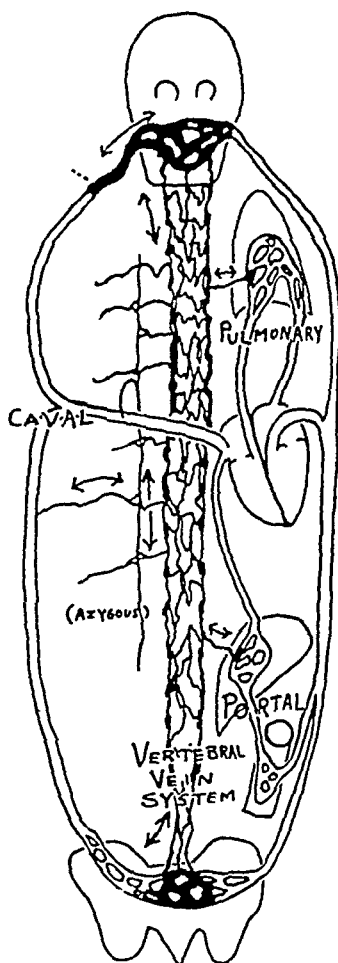


Fig. 3.—Schematic representation of the vertebral system and connections with other venous systems. (From Batson, Oscar V.: *Ann. Surg.* 112: 138, 1940.)

SUMMARY AND CONCLUSION

Injection experiments, according to the technique of Batson, were performed on cadavers by injecting the dorsal vein of the penis. Results similar to those reported by Batson were obtained. It is therefore concluded, with Batson, Bock, Cruveilhier, and others, that there is a fourth system of veins, namely, the vertebral or meningeorachidian system in addition to the caval, portal, and pulmonary systems, through which tumor cells or infected emboli are sometimes spread to distant parts; that these veins are of the primitive type, having no valves and carry-

ing the blood at low pressures which enables reversal of flow under certain circumstances, such as posture, coughing, sneezing, and straining; that this system of veins furnishes an anatomic explanation for the so-called "paradoxical metastasis." It is further concluded that the vertebral system of veins furnishes channels through which blood returns to the heart when large venous structures such as the femoral or iliac veins are occluded.

I wish to thank Dr. Robert Stone Dow, professor of Anatomy, University of Oregon Medical School, Portland, Oreg., for valuable suggestions in preparation of this paper. Also, I wish to thank the King County Hospital, Seattle, for making material available for this study.

REFERENCES

1. Litten, M.: Virchows Arch. 80: 281, 1880; quoted by Harris.⁷
2. Cohnheim, J.: Lectures on General Pathology, 1889, pp. 1-183; quoted by Harris.⁷
3. Warren, S., Harris, P. N., and Graves, R. C.: Osseous Metastasis of Carcinoma of the Prostate With Special Reference to Perineural Lymphatics, Arch. Path. 22: 139-160, 1936.
4. Batson, Oscar V.: The Function of the Vertebral Veins and Their Role in the Spread of Metastasis, Ann. Surg. 112: 138-149, 1940.
5. Batson, Oscar V.: The Role of the Vertebral Veins in Metastatic Processes, Ann. Int. Med. 16: 38-45, 1942.
6. Batson, Oscar V.: The Vertebral Vein System as a Mechanism for the Spread of Metastases, Am. J. Roentgenol. 48: 715-718, 1942.
7. Harris, H. A.: A Note on the Clinical Anatomy of the Veins With Special Reference to the Spinal Veins, Brain 64: 291-300, 1941.
8. Franklin, Kenneth J.: A Monograph on Veins, Springfield, Ill., 1937, Charles C Thomas, Publisher.
9. Bock, A. C.: Darstellung der Venen, Leipzig, 1823; quoted by Harris.⁷
10. Willis: Cerebrie Anatomie, 1664; quoted by Harris.⁷
11. Winslow: Exposition Anatomique, 1732; quoted by Harris.⁷
12. Breschet, G.: Recherches anatomiques, physiologiques et pathologiques sur le systeme veneux, Paris, 1832; quoted by Harris.⁷
13. Cruveilhier: Anatomie descriptive, vol. 3, Paris, 1834, p. 328; quoted by Harris.⁷
14. Hilton, J.: Development of Functional Relations of Certain Portions of the Cranium, London, 1855; quoted by Harris.⁷
15. Hamilton, W. F., Woodbury, R. A., and Harper, H. T. Jr.: Physiologic Relationships Between Intrathoracic, Intraspinal, and Arterial Pressures, J. A. M. A. 107: 853-856, 1936.
16. Lee, Ferdinand C.: Establishment of Collateral Circulation Following Ligation of Thoracic Duct, Bull. Johns Hopkins Hosp. 33: 21-31, 1922.
17. Martin, J. P.: Thrombosis in Superior Longitudinal Sinus Following Child-birth, Brit. M. J. 2: 537-540, 1941.

HOMOGENOUS CARTILAGE GRAFTS

AN EXPERIMENTAL STUDY

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(From the Department of Surgery, the University of Rochester School of Medicine and Dentistry)

AS I have previously reported there is some confusion regarding the viability of various types of cartilage transplants. Because of varying opinions and so-called "refrigerated isografts" I undertook an experimental study of autogenous cartilage grafts in dogs.¹ From that experiment, which was in agreement with previous experimental evidence and clinical impressions, it appeared that autogenous costal cartilage, when transplanted to the subcutaneous tissues in dogs, remained viable and did not lose weight or volume up to as long as one and one-half years. Whether the cartilage was transplanted with or without perichondrium did not alter the facts.

Since that time I have secured another bit of human experimental evidence which completely corroborates that experiment. A woman came in for advice concerning an asymmetry of the nose. Twelve years before, an autogenous costal cartilage graft had been used to correct a traumatic saddle-nose deformity. In correcting the asymmetry it was necessary to remove the previous graft for reshaping and a portion was saved for microscopic section. This showed normal appearing hyaline cartilage.

I think one can safely state that the evidence is incontrovertible that autogenous hyaline cartilage grafts retain normal gross and microscopic appearance for long periods. Moreover, degenerative changes are but little, if at all, accelerated by transplantation.

On the other hand, the data concerning the survival of homogenous cartilage grafts is quite meager. There are a few clinical reports. In 1937 Gillies² attempted and reported the successful transplantation of the cartilage framework of an ear from a mother to her son. J. B. Brown,³ in 1940, reported clinically successful cases of rib cartilage transplants from father and mother to sons, in the correction of traumatic facial deformities. However, since specimens have not been removed later for examination, one has no proof that these transplants do not actually die and remain merely as foreign bodies.

The experimental evidence is conflicting. Loeb and Siebert,^{4, 5} in the course of studies concerned with the transplantation of various tissues, state that there is greater tissue reaction to, and more eventual absorption of, homogenous cartilage grafts than of autogenous.

Kirkham⁶ found that auricular cartilage removed from one rabbit and placed in the abdominal subcutaneous tissues of another retained

its size and form but on section the cell spaces were vacuolated and nuclei absent. It should be stated that these experiments were an attempt to discover how long after death a homogenous cartilage transplant was possible. A rabbit was killed and one hour later a piece of ear cartilage was removed and placed in the abdominal wall of a living rabbit. At hourly intervals up to six hours another piece was removed and transplanted to another living rabbit. The transplants were removed in six months and examined.

From this experiment Kirkham concluded that cellular death of the transplants occurred but their form was retained. As will be seen, the experiment here reported disagrees with these findings.

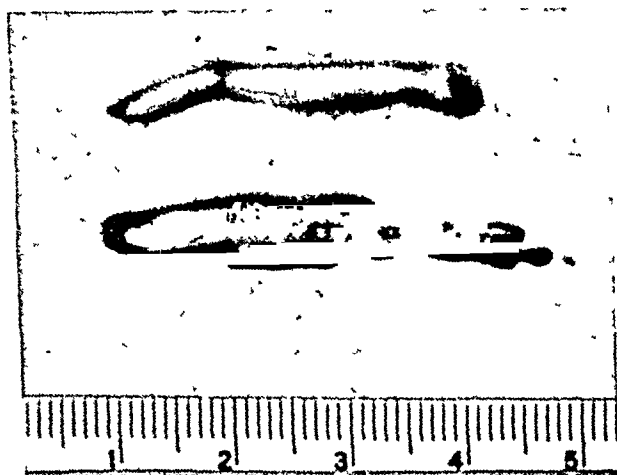


Fig. 1.—Homogenous costal cartilage removed from the abdominal wall of a dog one and one-half years old. Note the glistening translucent sheen of normal-appearing

cartilage.

METHOD OF EXPERIMENT

The same general method was used as in experimental transplantation of autogenous cartilage, except that two dogs were anesthetized and segments of costal cartilage removed from one were transplanted at once to the abdominal wall of the other. Five pairs of dogs were used.

In each instance care was taken to secure cartilage as nearly free from central ossification as possible. This must be kept in mind as central ossification of rib cartilage takes place quite early in dogs. The cartilage was removed through an oblique incision over the costal margins and cut into segments about one and one-half inches long. These were measured and then inserted into the abdominal subcutaneous tissues of the other animal through small incisions just to the right and left of the midline. Six pieces were implanted in the abdominal wall of each animal, three on the right, and three on the left. In this experiment soft tissues were removed from the transplant but no attempt was made to strip off the perichondrium, since in previous work it was

found that the presence or absence of perichondrium had no effect on survival of autogenous cartilage grafts. The various incisions were closed with silk.

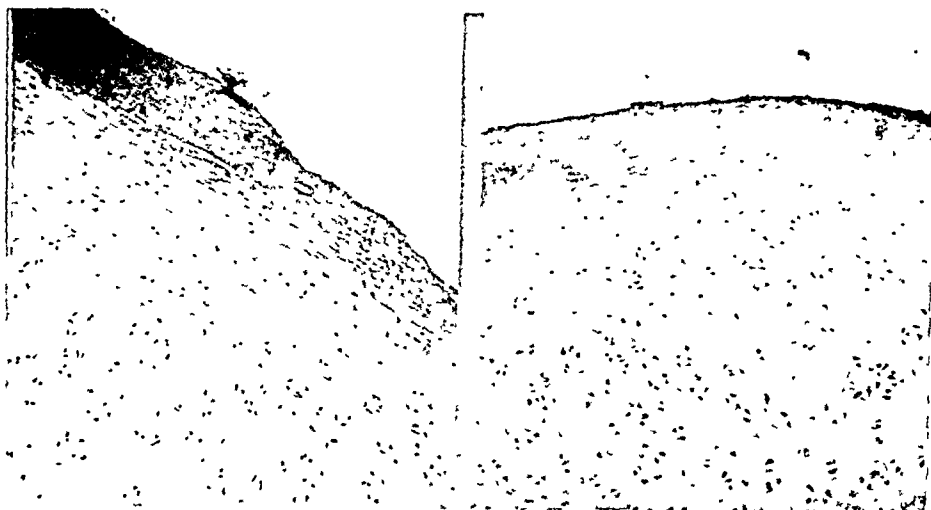


Fig. 2.—Photomicrographs ($\times 100$) showing the architecture normally seen in costal cartilage of young adult dog.



Fig. 3.—Photomicrograph ($\times 100$) showing homogenous costal cartilage two weeks after cross transplantation to abdominal subcutaneous tissues.

Thus, sixty pieces of costal cartilage were implanted in the abdominal walls of ten dogs, in each instance the cartilage being obtained from a donor dog. These grafts were then removed from a pair of dogs at intervals. In this way twelve grafts were removed at two weeks, three months, six months, one year, and one and one-half years.

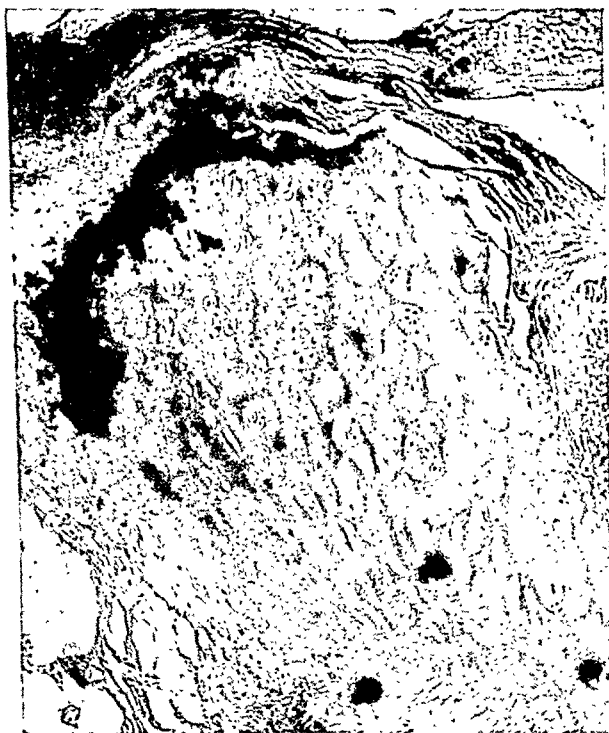


Fig. 4.—Photomicrograph (X100) showing homogenous costal cartilage graft removed after three months in abdominal wall. The cell architecture is normal.

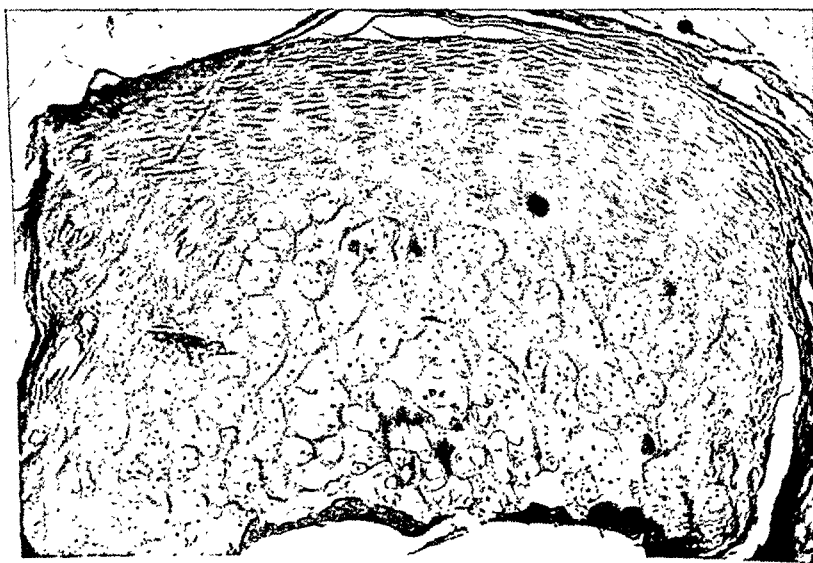


Fig. 5.—Photomicrograph (X100) showing homogenous costal cartilage transplant removed from abdominal wall after six months. There is moderate increase in the clear zones of the cells and a few cells without nuclei.

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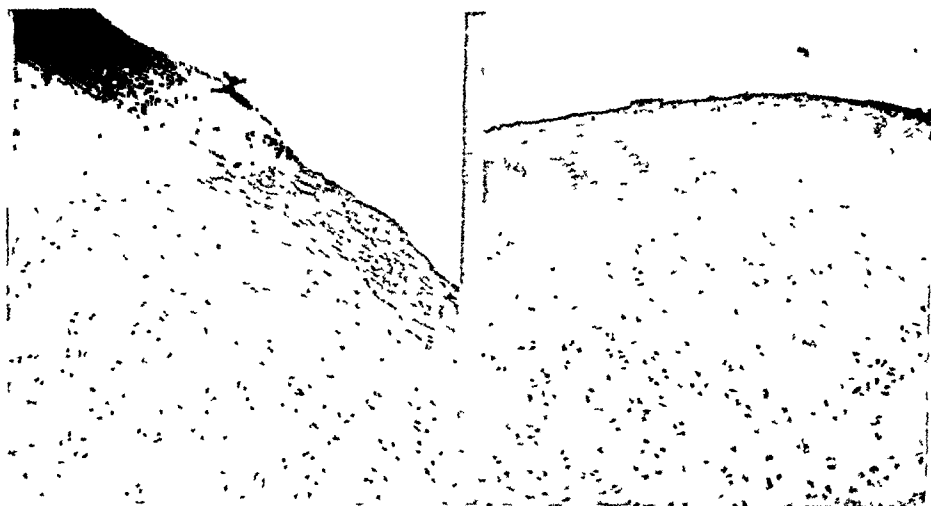


Fig. 2—Photomicrographs ($\times 100$) showing the architecture normally seen in costal cartilage of young adult dog.

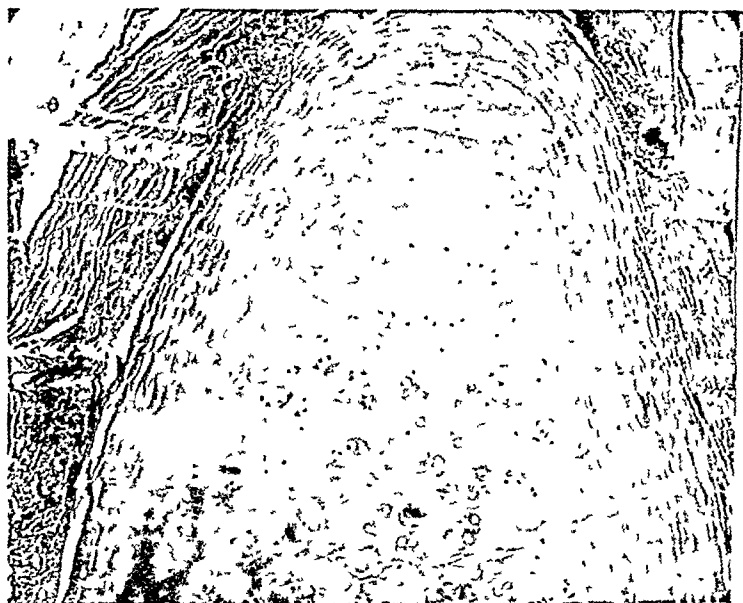


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GROSS EXAMINATION AND MEASUREMENT OF TRANSPLANTS

During the time the grafts were in place in the abdominal wall they could be felt and, in most instances, seen. Of the sixty pieces transplanted, all but two were recovered and examined. These two may not have been absorbed but may have migrated to a spot where they were not discovered, since it was noted that there was a tendency for the grafts gradually to change location.

On removal the transplants were firmly attached to the soft tissues without noticeable inflammatory or fibrotic reaction about them. They were removed by sharp dissection and cleared of soft tissues. They retained their cartilaginous appearance and springlike physical properties. In some instances softened yellowish spots were present which were thought to be areas of degeneration. The grafts were measured and it was found that there was no significant change in size.

All the recovered transplants were sectioned and examined microscopically. The accompanying photomicrographs (Figs. 1 to 7) are representative ones selected at the various time intervals. I believe that if presence of normal cartilaginous architecture is a criterion that one can state without hesitation, these cross-transplants remain viable. It is true that degenerative changes are present in that the clear zones around the nuclei are larger and central ossification is present. However, in interpreting this, one must remember that the ossification of costal cartilage in dogs is an early occurrence, and that in some instances early central ossification was already present when the transplants were carried out.

CONCLUSIONS

From this experiment it appears that costal cartilage can be transplanted from one dog to the subcutaneous tissues of another dog and remain viable in its new location up to one and one-half years.

REFERENCES

1. Young, Forrest: Autogenous Cartilage Grafts, *SURGERY* 10: 7, 1941.
2. Gillies, Sir Harold: Reconstruction of the External Ear With Special Reference to the Use of Maternal Ear Cartilage as the Supporting Structure, *Rev. de chir. structurive* 3: 169, 1937.
3. Brown, J. B.: Preserved and Fresh Homotransplants of Cartilage, *Surg., Gynec. & Obst.* 70: 1079, 1940.
4. Loeb, Leo: Autotransplantation and Homoiotransplantation of Cartilage in the Guinea Pig, *Am. J. Path.* 2: 111, 1926.
5. Loeb, Leo, and Siebert, W. J.: Transplantation of Skin and Cartilage in Chickens, *Arch. Path.* 20: 28, 1935.
6. Kirkham, H. L. D.: The Use of Preserved Cartilage in Ear Reconstruction, *Ann. Surg.* 111: 896, 1940.



Fig. 6.—Photomicrograph ($\times 100$) showing specimen removed after one year in abdominal subcutaneous tissues of recipient dog. The cells are well preserved. A central marrow cavity is present.



Fig. 7.—Photomicrograph ($\times 100$) showing a specimen removed one and one-half years after cross transplantation. This particular one was selected because it showed as marked central bone formation as any examined. Some specimens at one and one-half years showed relatively little.

1939, Everhart and Jacobs⁷ reported a case of right chylothorax in a newborn infant, thought to be due to trauma during delivery. They collected five such cases in infants under 1 year of age and four cases in those from 1 to 14 years, the etiology being either trauma or rupture secondary to obstruction by tuberculous nodes. Chylothorax caused by nodes were likely pseudochylous rather than true chylothorax. Beatty,² in 1936, reported a case of right chylothorax which developed six and one-half years after depressed fracture of the left clavicle. This is the longest reported interval between the trauma and the appearance of the lesion, but there was evidence of deformity of the subclavian vein and the chylothorax was doubtless due to the obstruction rather than direct trauma to the duct, however, both factors may have played a part.

In contradistinction to nonpenetrating injuries in which the lesion is usually on the right side, in penetrating wounds of the thorax the left side is more frequently involved (nine of fourteen, Shackelford and Fisher).¹⁷ Right chylothorax was the result of closed injuries in eighteen cases and open injuries in two cases. It is suggested that an injury low in the thorax results in a right-sided chylothorax and that a high injury causes a left chylothorax.¹⁷ Watts²¹ reported a case of self-inflicted knife wound of the suprasternal notch which severed the thoracic duct (proved at autopsy) and resulted in left chylothorax. Bullet wounds also have resulted in severance of the thoracic duct. Matson and Stacy¹⁵ reported a bullet wound of the duct successfully treated. The thoracic duct also has been injured surgically. Smith and Woliver¹⁸ report a case which followed resection of the right tenth rib for sarcoma. Turbid fluid was noticed in the wound near the end of the operation, the duct was not seen or ligated, several thoracenteses were done, and four intravenous injections of the fluid were given; the patient survived.

Clinically, in the patient with chylothorax there is a relatively asymptomatic interval between the trauma and onset of marked dyspnea, pallor, cyanosis, thready pulse, and shock. This period averages four days,¹⁴ during which time the patient's only complaint may be mild chest pain. The longest time interval is that reported by Beatty,² of six and one-half years. Usually following thoracentesis, the dyspnea is relieved, the cyanosis disappears, and the shock is relieved. However, there is a rapid reaccumulation of the fluid and aspiration must be repeated, sometimes within twelve hours. There is rapidly progressive loss of weight and emaciation. Physical examination at the onset reveals a dyspneic patient with weak pulse and low blood pressure; there is evidence of fluid in the pleural cavity. These findings are present each time the fluid reaccumulates.

A definite diagnosis is made by examination of the fluid which is milky in appearance. However, the first thoracentesis may yield milky

TRAUMATIC CHYLOTHORAX

REPORT OF A FATAL CASE COMPLICATED BY A RUPTURED DUODENAL ULCER

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The Charity Hospital of Louisiana)*

CHYLOTHORAX resulting from rupture of the thoracic duct due to trauma is an unusual condition which presents a challenging therapeutic problem. Dorsey and Morris,² in 1943, reviewed fifty-eight cases from the literature and reported one additional case. Doubtless, there are many unreported cases. Prognosis is grave since there is a 50 per cent mortality in cases in which operation has not been done, and direct surgery to repair the duct has been completely unsuccessful, resulting in 100 per cent operative mortality.

Traumatic chylothorax is often associated with fractured rib, fractured vertebra, or dislocation of vertebral bodies. However, it is not uncommon to find chylothorax following nonpenetrating injuries unassociated with any bone or joint injury which is demonstrable by clinical roentgenologic or post-mortem examination.

Frequently there is a history of the patient having fallen or being thrown on the back or having been in an auto accident where there is sudden hyperextension of the spine. The mechanism in such instances is thought to be that of stretching the thoracic duct and because the cisterna chyli is fixed beneath the diaphragm, rupture ensues.³ Following rupture, chyle escapes retropleurally and, later, the pleura ruptures, causing chylothorax as found at autopsy by Cellan-Jones and Murphy.⁴ In 1932, MacNab and Scarlett¹⁴ drained, by thoracotomy, a retropleural cavity which at post mortem was seen to communicate with the pleural cavity. The most frequent site of rupture in nonpenetrating injuries is in the supradiaphragmatic portion in the region of the ninth to tenth thoracic vertebrae, and leakage is usually into the right pleural cavity, since the duct at this level is on the right side and does not cross to the left side until the level of the seventh thoracic vertebra is reached. Of twenty-eight cases reviewed by MacNab and Scarlett,¹⁴ chylothorax was on the right in fifteen, on the left in eight, and on both sides in five. Shackelford and Fisher¹⁷ suggest that rupture may be due to increased intrathoracic pressure, but in discussing their paper Penick stated that valves in the thoracic duct are inefficient and that any extraductal pressure would force fluid in two directions and not increase tension on the duct wall. The former authors¹⁷ also point out that several cases have followed ingestion of a heavy meal, possibly because the intraductal pressure is highest at this time. In

Review of Recent Meetings

FIFTY-SIXTH ANNUAL MEETING OF SOUTHERN SURGICAL ASSOCIATION

GEORGE D. LILLY, M.D., MIAMI, FLA.

The fifty-sixth annual session of the Southern Surgical Association was held at the Homestead Hotel, Hot Springs, Va., Dec. 5, 6, and 7, 1914. Alton Ochsner and Alfred Blalock served as secretary. I. A. Bigger was chairman of the committee on Arrangements.

Dr. Arnold Griswold began the scientific program by presenting a discussion on **Unusual Lesions of the Stomach**. Several cases were presented in which ulcers were encountered in the proximal portion of the stomach. The adoption of a transthoracic approach to such lesions was demonstrated. It was pointed out that an approach through the left tenth rib bed, with splitting of the diaphragm and of the phrenic nerve, offered excellent exposure of this surgically inaccessible region. Infection was not encountered frequently, and the additional cost seemed to be worth while because of the better exposure.

Dr. Rienhoff analyzed **The Results of the Surgical Treatment of Peptic Ulcer of the Duodenum in a Series of 260 Cases**. Intractable pain, repeated hemorrhaging and vomiting were conditions which made surgery desirable. A Polya gastrectomy with resection was employed, with removal of one-third of the stomach and anastomosis. He reported that 78 per cent of the patients in this series were cured, 12 per cent improved, 8 per cent failed to improve, and 2 per cent had postoperative hemorrhage and 8 per cent developed

Dr. Marshall presented **A Plan for the Management of Gastrojejunal Ulcer**. Reviewing the literature on this subject, mortality rates ranging from 25 to 50 per cent were encountered. Most deaths were attributed to shock, hemorrhage, and perforation. It was observed that most of the fourteen cases studied developed ulcers of the gastroenterostomy. First, a jejunal ulcer developed, and then a duodenal ulcer. The greatest mortality was found to result from a single perforation. Dr. Marshall believes it is safer to do a radical two-third resection, the terminal ileum is anastomosed to the descending colon, and the transverse colon is resected. In one case the second anastomosis was necessary. There was one death in this series of fourteen cases.

Dr. Harry J. Warthen outlined **A Plan for Handling Emergency Cases in Force Hospitals**. Rooms were set up with full equipment which enabled those not too experienced to handle this type of work to do so. Dr. Warthen pointed out that such emergencies could be adapted to any hospital.

Dr. Alfred B. Standa, Jr., and Major W. H. L. Clark discussed **Aviation Medicine**. The subject was analyzed. It was found that

Major W. H. L. Clark discussed **Aviation Medicine**. The subject was analyzed. It was found that

Fat-free diet has been found to result in no reduction in the amount of fluid aspirated from the patient was put on fat-free diet.

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Immediate after operation, parenteral methods of nutrition include:

(1) the use of plasma in sufficient amounts, combined with (2) transfusions of whole blood. A combination of the two seems to answer the purpose better than either one alone. In addition, the fluid balance is kept up by glucose and saline infusions, to which solu-B (vitamin B) can be advantageously added. In accordance with the excess loss through the ileostomy, large quantities of fluid are needed, up to 4,000 to 5,000 c.c. daily, but the danger of overloading the vascular apparatus should be kept in mind in these otherwise debilitated patients. I have formed the habit of adding to each 1,000 c.c. of infusion 30 Gm. of aminoids (protein hydrolysate) and have found this of great use.

As soon as possible, oral feeding is instituted and increased as follows:

1. The dietary protein intake is increased to 150 to 180 Gm. per day. Usually the patient will not or cannot take more by mouth.

2. Gastric intubation is used, if possible. This may add as much as 50 per cent. But if too much is given, distention results, the patients develop diarrhea, and much protein is lost.

If, owing to digestive or other disability, the amount of protein is not sufficient, the discrepancy should be made good by adding a sufficient quantity of amino acids dissolved in, or mixed with, the food. This is easily done in the mouth feeding, and even more easily accomplished by intubation.

In the beginning, it is usually necessary to bolster the oral feeding with parenteral alimentation either by plasma or by whole blood, and this should not be avoided until the oral method is firmly established and is sufficient.

Later and after the patient leaves the hospital, excess and enriched protein nutrition should be continued for the reason that the ileostomy continues to discharge abundantly, and much is lost before complete utilization. Occasionally, even at this later period, bolstering up with parenteral methods is necessary—plasma, blood, and transudate fluids (ascitic or pleural). The last is a valuable method and decreases the expense.

At all stages of the postoperative care, alimentation, either oral or parenteral, must not exceed the toleration of the individual patient, otherwise the purpose would be defeated, much harm would be done, and convalescence from the operation would be interrupted.

At all stages of treatment, protein hydrolysates in the form of aminoids form a valuable addition to oral or parenteral alimentation. In the early stages, it can be used parenterally by adding the aminoids to the infusions as indicated previously. Later, aminoids can be added to the diet to enrich the protein stores. In long-standing cases of undernutrition, the oral use of these preparations finds an important and chief place.

SURGERY

Vol. 17

MAY, 1945

No. 5

Original Communications

Symposium on the Ulcer Problem

A DIRECT VISUAL TECHNIQUE FOR STUDYING CHEMICAL AND OTHER INJURY TO EXPOSED MUCOSAL SURFACES

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MOST of the techniques devised to study the enzymatic hydrolytic effects of gastric juice upon the mucosa of the alimentary tract have failed to provide means of studying the early and the progressive effects of such chemical injury. The technique herein described is directed at assaying the early effects of such injury. The accessibility of the exteriorized segment to direct vision and continued inspection provides a satisfactory means of studying the chemical injury attending the dripping of various solutions upon such exteriorized segments.

METHOD

Pedicle segments of the gastrointestinal tract are brought out and exteriorized upon the anterior abdominal wall of dogs. The reactions of these mucosal grafts to the constituents of gastric juice, interference with circulation, or trauma of any nature may be observed directly and dynamically. Serial photographs and biopsies of observed anatomic changes may be obtained. Two objections to the technique are alteration of the environment of the intestinal mucosa and the exposure of the mucosa to trauma other than that employed in the experiments. Acute experiments performed on freshly exteriorized segments eliminate largely the latter disadvantage. Experiments of four to twelve hours' duration have been employed to study the immediate and early effects of gastric juice dripped on intestinal mucosa. When the observation of the late effects of this chemical trauma is to be observed, a permanent pedicle flap graft of intestinal mucosa is employed.

TECHNIQUE OF PREPARING THE EXTERIORIZED SEGMENT

Under intravenous sodium pentobarbital anesthesia, employing 15 mg. per pound of dog, using strict surgical technique, a laparotomy is performed through a midline incision. The desired segment of gut is located. A loop with a good blood supply is chosen and it is divided at

Received for publication, Nov. 20, 1944.

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two points, four or five inches apart, between hemostatic forceps. The mesentery is divided down to its base in the nearest avascular areas below the two points of division, care being observed to protect the blood vessels to the isolated segment. In the acute experiments the open ends of the intestine are ligated with a heavy ligature. The isolated loop with blood supply intact is brought out upon the abdominal wall. The skin is loosely sutured around the pedicle, care being taken to avoid interference with the blood supply. The exteriorized intestinal segment is opened along the antimesenteric border and the corners are anchored to the skin of the abdominal wall by means of sutures. If protracted observations are to be carried out, one must re-establish the continuity of the intestine by means of an aseptic end-to-end anastomosis made over appropriate clamps. The isolated pedicled loop with blood supply intact is brought out through the skin incision and is opened along the antimesenteric border. A defect equal in area to the size of the opened bowel segment is made in the skin surrounding the laparotomy incision. Hemostasis is secured. The bowel segment is then sutured in the skin defect forming a pedicled flap graft of intestinal mucosa in the anterior abdominal wall of the dog. Sulfanilamide is spread over the site of anastomosis between the gut segment and the abdominal wall.

Employing this technique, it has been possible to exteriorize segments from all divisions of the gastrointestinal tract. However, due to the shortness of the common bile duct in the dog, it has been difficult to exteriorize the gastric antrum and the first portion of the duodenum. However, if the common bile duct is ligated and divided, these segments can be brought out. For acute experiments, no effort is made to re-establish re-entry of the bile into the intestinal canal. For protracted observations, a cholecystoenterostomy may be performed.

With a slight modification of technique, a preparation may be made in which vascular phenomena can be studied. The mesentery of the gut is pulled over to one side and tacked between the skin and the edge of the opened intestine. The arteries subsequently may be dissected out, and the effects of emboli or medicaments injected through a fine caliber needle may be noted.

The reactions of these mucosal segments are studied as follows: The dogs being anesthetized are secured to a wooden frame in the supine position. The experimental solutions are then dripped on the mucosa and the reactions observed as they progress. The tissue may be photographed and biopsies may be taken at any time.

This method of studying the effects on isolated exteriorized segments of gastric juice, obtained from dogs with isolated pouches under histamine stimulation as well as hydrochloric acid with or without the addition of pepsin, dripped at a constant rate upon the exteriorized segment suggest definitely that all segments of the gastrointestinal canal are susceptible of injury by this means with 0.1 normal hydrochloric acid. The importance of pepsin in augmenting the injury produced by hydrochloric acid is obvious, as is also the effect of trauma to the exteriorized mucosa.

Fig. 1 demonstrates the progressive damage to duodenal and antral mucosa produced by dripping on an isotonic acid solution of pH 1.2

at one point on both the antrum and the duodenum and acid gastric juice (pH 1.12) obtained from a histamine-stimulated Heidenhain pouch on another for a period of three and one-half hours. The enhancement of degree of mucosal destruction by trauma induced by gently stroking

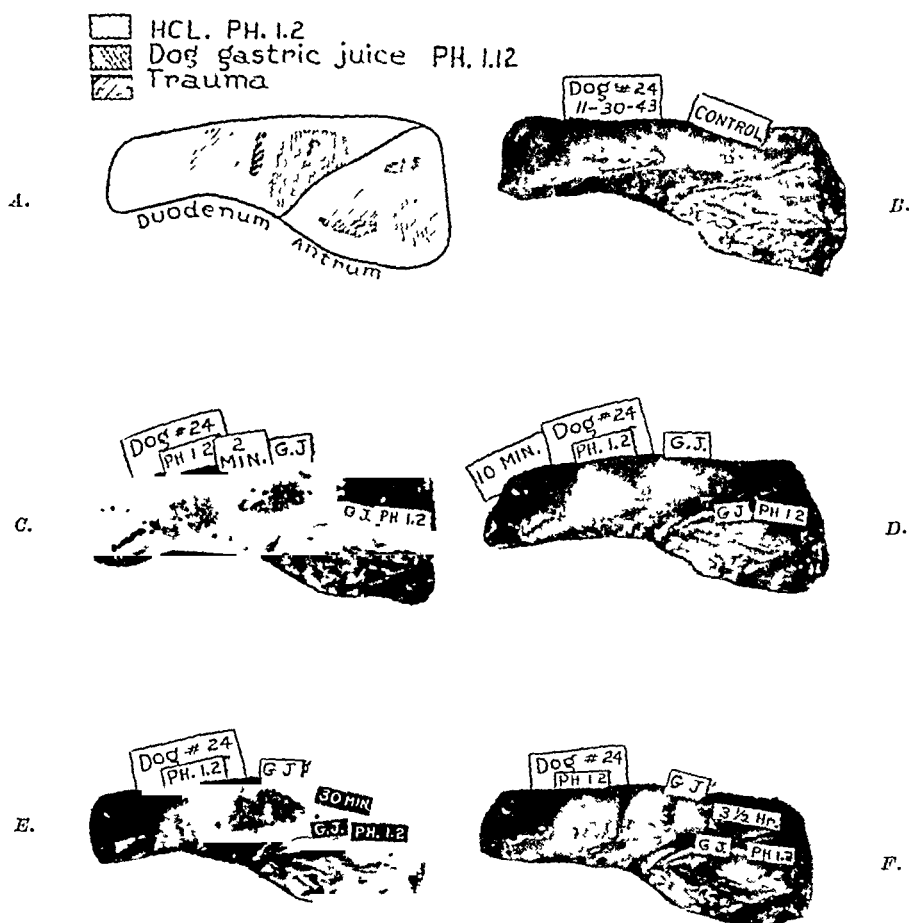


Fig. 1.—Experimental Dog 24. Photographic series revealing chronologically the alterations in exteriorized gastric antral and duodenal mucosa of a dog exposed to an isotonic hydrochloric acid solution of pH 1.2 and to dogs' gastric juice of pH 1.12 obtained from histamine-stimulated Heidenhain pouches. The effect of trauma in the normal mucosa and that damaged by the gastric juice induced by stroking it every five minutes with the rubber eraser of a pencil is also shown.

A, Topographic map designating areas of antral and duodenal mucosa dipped with hydrochloric acid and gastric juice. The regions traumatized are also revealed.

B, Control reveals character of mucosa of the opened exteriorized gastric antrum and duodenum.

C, Alterations two minutes after dripping designated areas with the isotonic hydrochloric acid solution pH 1.2 and the dogs' gastric juice (pH 1.12). Antrum reveals no damage in either area. Duodenal mucosa has reacted in this short time to both solutions by marked edema and gray discoloration of the mucosa.

D, Alterations within ten minutes. Antral mucosa shows no effect. Duodenal mucosa has become increasingly edematous and a superficial gray exudate has appeared in both areas.

E, Alterations within thirty minutes. Antral mucosa still resists corrosive action of both gastric juice and the acid as well as trauma. The duodenal mucosa is markedly damaged with an increase in the intensity of the edema, exudate and now superficial necrosis is present at both regions but slightly greater in the area exposed to gastric juice. Trauma has caused a slight erythema barely perceptible in the photograph in the normal mucosa in contrast to erosion and small petechial hemorrhages in region exposed to gastric juice.

F, Alterations after three and one-half hours' exposure. The antral mucosa has resisted the acid solution of pH 1.2 as well as trauma alone. Spontaneous petechial hemorrhages occurred in region exposed to gastric juice after two hours and increased up to this point. Traumatization caused superficial erosion and increased the area damaged by gastric juice. The duodenal mucosa has been damaged by both the acid and the gastric juice. The exudation and necrosis caused by the effects of the latter. Traumatization of the normal mucosa caused increased erythema and some extravasation of blood. A hemorrhagic ulcer in the region damaged by gastric

the regions exposed to gastric juice is obvious. Duodenal damage consists of progressive edema and necrosis and commences within two minutes, progressing very rapidly in both exposed areas. The antral mucosa is much more resistant, as it shows no tendency to necrosis or ulceration in the area exposed to the acid or trauma alone. On the other hand, petechial hemorrhages occurred in the area exposed to gastric juice after two hours. Trauma caused ulceration and hemorrhage in the damaged duodenal mucosa and only hemorrhage in the damaged antral mucosa.

It is proposed to attempt to determine the susceptibility of various segments of the gastrointestinal canal to such chemical injury.

CONCLUSION

A method of studying the effects of chemical and other types of trauma to various segments of the gastrointestinal canal is described. The celerity with which evidences of mucosal injury appear, attending the dripping of solutions of hydrochloric acid within the physiologic range upon exteriorized segments, is striking. The deleterious effect of local trauma is apparent.

THE PATHOGENESIS OF CAFFEINE-INDUCED ULCERS

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INTRODUCTION

THE observation of Judd¹ on the production of acute and subacute gastric ulcers in cats by the intramuscular implantation of caffeine in a beeswax-mineral oil mixture was recently confirmed by us.² A hypothetical analysis of the pathogenesis of the caffeine-induced ulcer was presented. Since then we have demonstrated that caffeine is a potent stimulus for the secretion of acid and pepsin.^{3, 4} In addition it was noted that when histamine and caffeine were given alternately, acute bleeding erosions and ulcers could be observed to develop during a period of five or seven hours. This rendered it possible to study the pathologic histogenesis of these ulcers in considerable detail.

In this paper we shall report the vascular changes in the gastric mucosa produced by caffeine, and elaborate upon the other factors in the pathogenesis of caffeine-induced ulcer.

METHODS

In eight acute experiments with cats under light chloroform anesthesia, an incision was made through the serosa, muscularis, and mucosa of a relatively avascular area of the stomach. The mucosa everted, forming a stoma which was protected and kept moist by normal saline solution. After a control period of fifteen minutes during which time the

red intensity of the mucosa was estimated in comparison with a Tallqvist hemoglobin scale.⁷ several small sections of the stomach wall were cut from the free edge and fixed immediately in formaldehyde for microscopic study. Then caffeine was slowly administered intravenously (250 mg. caffeine sodium benzoate), the intensity of redness was estimated, and sections of stomach wall were removed from an area adjacent to the control at fifteen-minute intervals for sixty to seventy-five minutes.

Control experiments were conducted using an equivalent amount of sodium benzoate (125 mg.) in an equal volume of physiologic saline solution (1 c.c.). Precautions were taken to keep manipulations of the stomach to a minimum. All of the animals were fasted ten to twelve hours previous to the experiments.

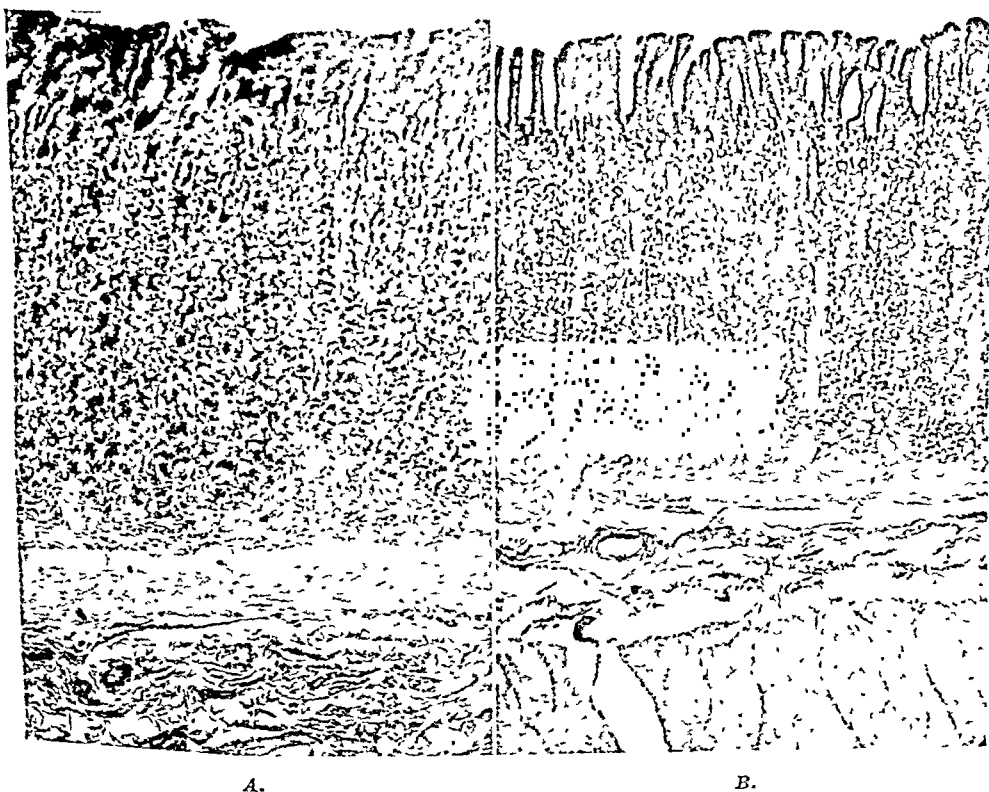


Fig. 1—Control. A, Photomicrograph of gastric mucosa before caffeine ($\times 145$). Note absence of vessels in the mucosa. B, Photomicrograph of gastric mucosa one hour after caffeine ($\times 80$). Note dilated and engorged venules in the mucosa and submucosa. Lower magnification was selected to show a larger field.

RESULTS

Direct observation of the gastric mucosal stoma in the cat showed a persistent reddening (hyperemia) after the intravenous administration of caffeine, followed in one hour by cyanosis. During the phase of hyperemia, the mucosa became thickened, moist, and succulent; the rugae became fuller and smoother. Kodachrome photography recorded these changes.

Fig. 1 shows the microscopic vascular changes following administration of caffeine. When the mucosa grossly appeared more reddened (an average change from 20 to 50 per cent on the Tallqvist scale), the veins and venules of the submucosa appeared markedly dilated and engorged with blood. However, when the mucosa appeared cyanotic there was

marked dilatation and engorgement of the mucosal venules, which previously were not apparent to any great extent, and scattered collections of serous transudate and extravasated blood elements were observed. These gross and microscopic vascular changes suggest the following train of events: vasodilatation and engorgement, vascular stasis, local anoxia, increased capillary permeability, transudation, extravasation of blood elements, and decreased cell nutrition.

The mucosa in the control experiments did not show any similar vascular changes.

DISCUSSION

The central and peripheral actions of caffeine on the blood vessels are antagonistic. Caffeine tends to constrict blood vessels by stimulation of the medullary vasomotor center, and to dilate them by a direct effect on vascular musculature.⁶ Goodman and Gilman state that, "after therapeutic doses, the peripheral vasodilator action predominates. Oncometer studies in experimental animals show that there is a definite increase in organ volume following the administration of a xanthine." Early investigators reported an increased volume of the splanchnic and cerebral regions after stimulating doses of caffeine due to persistent vasodilatation.⁷⁻⁹ The present studies upon the gross and microscopic vascular changes induced by caffeine confirm the vasodilatation as specifically related to the gastric mucosa. A discussion of some of the factors which appear to be involved in the pathogenesis of caffeine-induced ulcers in cats follows.

We have suggested² that the proteolytic action of acid and pepsin secretion upon a gastric mucosa, rendered more susceptible to the ulcerative process by the vascular and "cellular" changes induced by caffeine, results in the development of an ulcer.

Caffeine and its related beverages have been shown to be potent stimulants of *both* the acid and pepsin content of gastric juice in man and the cat.^{3, 4, 10} Considerable evidence indicates that the excessive continuous secretion of gastric juice with relative or absolute deficient neutralization is one of the major factors in the pathogenesis of human gastroduodenal ulcers.¹¹ With this in mind and in order to produce ulcers experimentally, it was thought desirable to provoke the constant elaboration of gastric juice so that when the stomach was empty of food content a relative deficient neutralization would be obtained. Thus, in an attempt to obtain prolonged and continuous caffeine action, the technique of embedding caffeine in a beeswax-mineral oil mixture was used as in the experimental production of "histamine ulcers."^{12, 13}

Attention is called to the fact that when the histamine mixture was implanted subcutaneously, infectious abscesses almost invariably developed at the site of injection.¹⁴ It is conceivable that the decreased general resistance of the body that accompanies chronic infectious foci may play a contributory role in the pathogenesis of histamine-induced ulcers. It is a well-known clinical observation that recurrences of gastroduodenal ulcers are more frequent in the presence of focal infectious processes. However, it is unlikely that a similar factor is involved in the pathogenesis of "caffeine ulcers" inasmuch as no similar abscesses were observed when the caffeine mixture was implanted *intramuscularly*.

In recent years considerable emphasis has been placed upon the acid and pepsin factors, but opinion has been divided as to the relative importance of one over the other; hence the designations "peptic ulcer" and "acid ulcer." However, this is an artificial distinction since the proteolytic action of gastric juice is not due to acid or pepsin alone, but to pepsin in acid solution.¹⁵

The consensus today is that "ulcer of the stomach is in some way due to a *local loss of resistance* on the part of the mucous membrane to the digestant activity of the gastric juice."¹¹ This factor is too frequently overlooked in a consideration of the pathogenesis of spontaneous or experimentally induced ulcers; as a consequence, investigators have recently directed their attention and emphasis upon the importance of acid and/or pepsin to the exclusion of those *factors which increase the susceptibility of the mucosa* to the proteolytic action of acid and pepsin. Some of these factors with reference to caffeine will be discussed.

The microscopic picture suggests that the marked vasodilatation and engorgement might in turn give rise to stasis, increased capillary permeability, transudation, extravasation of formed blood elements, and impaired cell nutrition, all of which would contribute to the devitalization of the mucosa and the development of an ulcer. Babkin takes the position that the devitalizing mechanism is one of vasodilatation and stasis.¹⁵ Direct observation of a mucosal stoma in the cat shows a persistent blushing (hyperemia) after the intravenous administration of caffeine, followed by cyanosis.

Vascular changes in the gastric mucosa similar to those induced by caffeine in the cat have been observed in man under various conditions. In their experiments upon a modern "Alexis St. Martin," Wolf and Wolff⁵ observed that "intense anxiety, hostility and resentment were accompanied by severe and prolonged engorgement, hypermotility and hypersecretion in the stomach. In this state mucosal erosions and hemorrhages were readily induced by even the most trifling traumas and frequently bleeding points appeared spontaneously as the result of vigorous contractions of the stomach wall." Thus, a hyperemic succulent mucosa, whether provoked by emotional reactions or caffeine, is apparently "friable" and susceptible to the ulcerative process.

Continuous or repeated stimulation of gastric secretion in the anesthetized cat with histamine for ten to twelve hours produces no apparent change in the gastric mucosa.² But, if caffeine (250 mg. caffeine sodium benzoate, intravenously or by direct lavage of the stomach, for thirty minutes) is alternated with the histamine (0.3 mg.), large diffuse areas of epithelial desquamation, multiple bleeding erosions, and ulcerations of the gastric mucosa are observed in as short a time as five hours (Figs. 2 and 3). Since both caffeine and histamine stimulate the flow of an acid gastric juice and cause vasodilatation, and since histamine alone does not induce ulceration of the gastric mucosa in acute experiments, caffeine may provide an additional factor which contributes to the decreased resistance of the mucosa. This alteration in the susceptibility of the gastric mucosa to the proteolytic action of gastric juice has been arbitrarily designated and attributed to "cellular toxicity." This factor may involve alteration in cell permeability, the concept of caffeine-histamine synergism,¹⁶ or a more prolonged stimulation of pepsin than

that provoked by histamine.⁴ Schifffrin and Warren¹⁵ have shown that the incidence of experimentally induced ulcerations of the gastrointestinal tract is much higher by perfusion, with optimum concentrations of acid and pepsin than by perfusion with acid alone. Thus, the vascular



Fig. 2.—Acute experiment, gastric contents were continuously drained out through a pyloric cannula. Sequence of gastric stimulations: 0.5 mg. histamine, subcutaneously 100 mg. caffeine (lavage for thirty minutes), and 0.5 mg. histamine, subcutaneously. Duration of experiment seven hours. Note diffuse areas of superficial desquamation of epithelium, multiple bleeding erosions, and ulcerations of the gastric mucosa.



Fig. 3.—Photomicrograph of an acute erosion. Note superficial mucosal defect with fragmentation of the glandular epithelium, venule dilatation, engorgement, and thrombosed vessel.

changes and factor of "cellular toxicity" are implicated in the pathogenesis of caffeine-induced ulcers in cats by increasing the susceptibility of the mucosa to the digestive action of gastric juice.

In addition to the direct pharmacodynamic effects of caffeine upon the stomach, there may or may not be a *neurogenic* factor by virtue of the excitatory action of caffeine upon the central nervous system. It is a well-established clinical observation that the emotionally tense, con-

scientious, hard-working individuals generally constitute the ulcer diathesis. Also, prolonged resentment, hostility, and anxiety are commonly associated with recurrence or perpetuation of an ulcer. It is conceivable that the consumption of large quantities of caffeine-containing beverages might aggravate these neurogenic factors and thus contribute to a vicious cycle in their influence upon human gastroduodenal ulcers.

We have previously noted the species difference in the secretory response to caffeine;² gastric secretion is stimulated in man and in the cat, but not in the dog. An attempt was also made to produce ulcers in dogs by the intramuscular implantation of caffeine in beeswax and mineral oil, but no change was observed in the gastric or duodenal mucosa after daily injections over a period of three months. The explanation for this species difference is not apparent at present. The gastric mucosa of the cat appears to be more susceptible to ulceration than the duodenal mucosa; the incidence of "histamine ulcers" as well as "caffeine ulcers" in the gastric mucosa outnumbers those in the duodenal mucosa of the cat.^{1, 2, 13} The converse is true of the location of histamine-induced ulcers in the dog.¹³

Ivy¹⁷ concluded that, "if those reported failures of atropine, in doses adequate to cause complete xerostomia and disturbances of vision, to abolish the gastric secretory response to a meal in man are not due to the presence of an ulcer or a 'pre-ulcer' condition, then normal men have a gastric secretory mechanism not found in the normal dog." It is evident from the present studies on caffeine that normal man does possess a gastric secretory mechanism not found in the normal dog.

SUMMARY

Evidence is presented in support of some of the factors which appear to be involved in the pathogenesis of caffeine-induced ulcers. It is believed that the proteolytic action of acid and pepsin secretion upon a gastric mucosa, rendered more susceptible to the ulcerative process by the vascular and "cellular" changes induced by caffeine, results in the development of an ulcer.

REFERENCES

1. Judd, E. S., Jr.: *Bull. Am. Coll. Surgeons* 28: 46, 1943.
2. Roth, J. A., and Ivy, A. C.: *Gastroenterology* 2: 274, 1944.
3. Roth, J. A., and Ivy, A. C.: *Am. J. Physiol.* 141: 454, 1944.
4. Grossman, M. L., Roth, J. A., and Ivy, A. C.: *Gastroenterology*. (In press.)
5. Wolf, S., and Wolff, H.: *Human Gastric Function*, New York, 1943, Oxford University Press, J. A. M. A. 120: 670, 1942.
6. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Company, p. 277.
7. Phillips, J., and Bradford, J. R.: *J. Physiol.* 8: 117, 1887.
8. Gottlieb, R., and Magnus, R.: *Arch. f. exper. Path. u. Pharmacol.* 45: 223-248, 1901.
9. Loewi, O.: *Sitzungsb. Marburg*, July, 1904.
10. Roth, J. A., Ivy, A. C., and Atkinson, A. J.: *J. A. M. A.* 126: 814, 1944.
11. Dragstedt, L.: *Arch. Surg.* 44: 438, 1942.
12. Walpole, S. H., Varco, R. L., Code, C. F., and Wangenstein, O. H.: *Proc. Soc. Exper. Biol. & Med.* 44: 619, 1940.
13. Hay, L. J., Varco, R. L., Code, C. F., and Wangenstein, O. H.: *Surg., Gynec. & Obst.* 75: 170, 1942.
14. Shoch, D., and Grossman, M. I.: *Personal communication*.
15. Schiffrin, M. J., and Warren, A. A.: *Am. J. Digest. Dis.* 9: 205, 1942.
16. Roth, J. A., and Ivy, A. C.: *Am. J. Physiol.* 142: 107, 1944.
17. Ivy, A. C.: *SURGERY* 10: 861, 1941.
18. Babkin, B. P.: *Canad. M. A. J.* 38: 421, 1938.

INFLUENCE OF CAFFEINE ON ULCER GENESIS

EXPERIMENTAL PRODUCTION OF GASTRIC ULCER IN GUINEA PIGS AND CATS WITH CAFFEINE, TOGETHER WITH A STUDY OF ITS EFFECT UPON GASTRIC SECRETIONS IN DOG AND MAN

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INTRODUCTION

MAN appears to be "addicted" to various beverages containing methyl derivatives of xanthine. The most important ones are caffeine (trimethylxanthine), the principal alkaloid of coffee, tea, kola, etc., and theobromine from cacao. Certain popular soft drinks also contain substantial amounts of caffeine. A strong cup of coffee or tea contains 0.10 to 0.12 Gm. of caffeine. The well-known pharmacologic action of these drugs is essentially that of the alkaloid present.¹²

Because of (1) the widespread use of caffeine-containing beverages, (2) the limited tolerance of habitual consumers of caffeine, (3) the general acceptance of the doctrine that coffee and tea should be eliminated from the diet of the ulcer patient, and (4) the apparent confusion in the literature regarding the effect of caffeine on gastric secretion, it was suggested that a further evaluation of this problem should be made.

A few years ago (1940), the possible relationship of caffeine upon gastric secretion was brought to light in a rather striking manner. A young man was admitted to hospital with a perforated "peptic" ulcer. He gave a history of having ingested approximately 150 bottles of an iced kola drink over a period of five days during the heat of August. He gave no antecedent story of ulcer. Later, another patient presented himself experiencing extreme difficulty with a duodenal ulcer. A careful review of his habits revealed that he was a self-styled coca-cola "addict." In this latter case, the association of these two conditions may have been coincidental. However, in the first patient, it is difficult to set aside the possibility of a causal relationship. It was the observation of these two cases that suggested subjecting the caffeine influence in ulcer genesis to experimental scrutiny. A preliminary report was made from this clinic on the matter by Judd⁶ in 1942.

PREVIOUS STUDIES

In a review of the American and English literature, little work of primary importance has been done.

Allard¹ (1904) discovered at autopsy gastric hemorrhages and erosions in patients receiving Theocin, a proprietary name for synthetic theophylline having the same pharmacologic action as caffeine. Experimentally, in dogs he administered theocin by nasal tube. The dosage

The researches presented here were supported by grants of the Augustus L. Searle Fund for Experimental Surgical Research, the Citizens Aid Society, and the Zimmerman Fund for Surgical Research.

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varied from 0.29 to 0.76 Gm. per kilogram of body weight. In three to eleven days he noticed gastric hemorrhages and erosions; rabbits developed bleeding areas, cats only edema of the mucosa.

In 1906, Pineussohn⁸ observed a prompt rise in the free and total acid, as well as volume of gastric juice in dogs with Pavlov pouches given 300 c.c. of a coffee mixture containing 20 Gm. of coffee. Using cocoa, which contained only 15 per cent of its normal fat content, a slight increase in gastric acidity was evident. Tea (10 Gm. in 300 c.c. of water) was observed to decrease the pouch secretion.

Salant and Rieger¹¹ (1909) administered caffeine subcutaneously to dogs. Eleven centigrams were sufficient to kill the experimental animals. At autopsy "inflammation and ulceration of the intestines and especially of the stomach" were present.

In 1933 and 1934, Hanke^{3, 4, 5} was able to produce erosions in the esophagus, stomach, and duodenum using large hypodermic injections of caffeine in cats. He called these "immediate peptic ulcers." Subsequently, Hanke observed "chronic peptic ulcers" with caffeine by the daily subcutaneous injection of 200 to 300 mg. of caffeine sodiosalicylate. These ulcers were superimposed upon a severe gastritis. He noted that caffeine caused a sharp increase in the degree of gastric acidity and volume. He concluded that he was dealing with a "primary peptic gastritis occurring in a highly acid gastric juice. This powerful secretion leads to erosion."

Molteni,⁷ in 1938, noted ulcerative lesions in the rat when injected daily with 10 to 25 cg. of caffeine sodiosalicylate. When given smaller doses over a period of seventy days, 40 per cent of twenty-four rats developed ulcers. These lesions appeared in the antrum and pylorus. Molteni felt that the hyperacidity of the gastric juice was the principal, but not the only factor involved.

The studies reported herewith represent an amplification of the preliminary report of Judd⁶ (1942), the writing and publication of which work was suspended by the exigencies of the war.

Recently, Roth and Ivy^{9, 10} (1944) reported upon the effects of caffeine upon the gastric secretions in the dog, cat, and man. Caffeine sodium benzoate, 65 to 250 mg., was given by various routes. These investigators concluded that: (1) caffeine does not stimulate gastric secretion in the dog, (2) caffeine administered by the intravenous route or by lavage of the stomach provokes a copious flow of acid gastric juice in the cat, and (3) caffeine administered intramuscularly or orally stimulates gastric secretion in man.

METHODS OF STUDY AND RESULTS

I. *The Production of Ulcers in Guinea Pigs and Cats.*—First, a series of five guinea pigs was used. Daily, each experimental animal was injected intramuscularly with 200 mg. of caffeine alkaloid in beeswax. The preparation was in accord with the method described by Code and Vareo² for histamine in beeswax. Caffeine was substituted for histamine in their formula. The caffeine alkaloid in beeswax mixture was prepared freshly each day.

After the initial injection, the guinea pigs became lethargic, anorexic, and, in short, exhibited a severely toxic state. None of these animals survived the fifth injection (see Table I).

TABLE I
GUINEA PIGS

NO.	SURVIVAL DAYS	AUTOPSY RESULTS
1	3	Negative
2	3	Negative
3	5	Negative
4	3	Negative
5	4	Mild gastritis; moderate duodenitis

Dosage: 200 mg. of caffeine alkaloid in beeswax intramuscularly daily.
Average weight: 976 Gm.

Only one of the guinea pigs (Fig 5) showed any suggestive gastric pathology. Because of the drug toxicity in the dosage given and the short survival period, the results obtained are of little or no value. Consequently, the dosage was reduced. A series of ten guinea pigs was used. Daily these animals were injected intramuscularly with 100 mg. of caffeine alkaloid in beeswax. This mixture was prepared as previously described (see Table II).

TABLE II
GUINEA PIGS

NO.	SURVIVAL DAYS	AUTOPSY RESULTS
1	1	Negative
2	3	Shallow erosion 3 mm. in diameter; 8 mm. distal to pylorus
3	5	Shallow erosion in the fundus 3 mm. in diameter; a duodenal ulcer 3 mm. in diameter, 4 mm. distal to the pylorus
4	5	Multiple shallow hemorrhagic ulcers throughout the stomach but particularly in the corpus
5	7	Negative
6	10	3 small mucosal hemorrhages in the corpus; no ulcer
7	5	Shallow erosion in the pylorus
8	7	Multiple small mucosal antral hemorrhages; no ulcer
9	10	One small submucosal hemorrhage in the corpus; no ulcer
10	10	One small submucosal antral hemorrhage; no ulcer

Dosage: 100 mg. of caffeine alkaloid in beeswax intramuscularly daily.
Average weight: 890 Gm.

The survival time was prolonged somewhat and the incidence of gastroduodenal pathology was increased markedly. Eight of the ten guinea pigs (80 per cent) exhibited upper gastrointestinal pathology. These changes varied from small mucosal hemorrhages to definite ulcer production. Four of the guinea pigs (40 per cent) developed erosions or ulcers (see Fig. 1).

Next, a series of twenty-six cats similarly was injected daily with 300 mg. of caffeine alkaloid in beeswax. All injections were made intramuscularly. These animals tolerated the drug fairly well. Some hyperactivity and excitement were noted after the initial injections; however, terminally, a state of lethargy ensued. Fourteen of the twenty-six cats (53.9 per cent) exhibited gastric and/or duodenal pathology (see Table III).

Nine cats developed ulcers. These ulcers were punched out, sharply defined, and in several instances multiple lesions were present. The

lesions were similar in all respects to the "peptic" ulcers found in man (see Fig. 2).

II. *Studies on Dogs With Gastric Pouches.*—Desirous of establishing the effect of caffeine on gastric secretions, pouch dogs were injected subcutaneously with various doses of freshly prepared solutions of aqueous caffeine citrate and aqueous caffeine alkaloid. Both drugs are 50 per cent solutions of caffeine.

These pouch dogs had been standardized, fasting for five consecutive hours on three separate occasions. In this manner, a mean standard fasting curve was established for each animal. Routinely, food pans were removed seventeen hours prior to experiments, although water was allowed the dogs up until but not during the testing period. All dogs were given one or more days' rest between experiments. Identical diets were maintained on regular feeding schedules during the resting days.



Fig. 1.

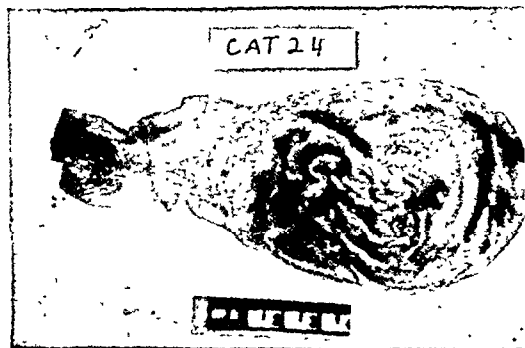


Fig. 2.

Fig. 1.—Guinea pig 4, Table II. Multiple shallow hemorrhagic ulcers were produced in the guinea pig throughout the entire stomach attending the daily intramuscular injection of 100 mg. of crude caffeine alkaloid in beeswax for five days.

Fig. 2.—Cat 24, Table III. This experimental animal was injected intramuscularly daily for twelve days with 300 mg. of crude caffeine alkaloid in beeswax. Several hemorrhagic erosions were present in the corpus of the stomach. The antrum revealed two punched out ulcers. In the duodenum, submucosal hemorrhages were observed.

In these experiments, pouch juice was collected under similar conditions for one hour, from 9 to 10 A.M., and this was used as the fasting sample for that experiment. Freshly prepared aqueous caffeine alkaloid (300 to 1,200 mg.) was injected subcutaneously. Subsequent hourly samples were collected in clean test tubes. No attempt was made to correlate dosage with body weight.

At the conclusion of the experiment, each hourly sample was titrated with 0.1 NaOH, using Toepfer's solution and phenolphthalein as indicators for free and total acid. Volumes were measured to .1 centimeter.

TABLE III

CATS

NO.	SURVIVAL DAYS	AUTOPSY RESULTS
1	23	Antral ulcer; duodenal ulcer
2	3	Linear antral ulcer
3	15	Negative
10	4	Negative
11	16	Multiple small hemorrhages in the fundus; 2 antral ulcers (4 mm.; 3 mm.)
12	22	3 linear antral erosions
13	24	Multiple long, deep linear ulcers in the corpus; 2 antral ulcers
14	28	Negative
15	4	Negative
16	14	Scattered duodenal petechiae; no ulcer
17	9	Negative
18	5	Negative
19	10	3 mm. shallow hemorrhagic antral ulcer; 2 tiny erosions about the ulcer
20	15	Negative
21	11	Multiple pinhead submucosal duodenal hemorrhages
22	6	Negative
23	19	3 irregular submucosal hemorrhages in the antrum
24	12	2 punched out antral ulcers (4 mm.; 5 mm.). Multiple small erosions in the corpus; submucosal duodenal hemorrhages
25	15	Negative
26	9	Severe hemorrhagic gastritis and scattered erosions in the corpus
27	11	Negative
28	8	Prepyloric ulcer
29	1	Negative
30	11	Multiple gastric ulcers; moderate gastritis
31	10	Antral ulcer; antral erosion
32	1	Negative

Dosage: 300 mg. of caffeine alkaloid in beeswax intramuscularly daily.

Average cat weight: 6.3 pounds.

Twenty-two experiments were performed on nine pouch dogs. A difference of 20 degrees of free acid between the dogs' fasting sample and the free acid during the subsequent four hours was arbitrarily chosen as our criterion for a stimulation or depression effect. In some experiments, the variation of free acid was less than plus or minus 20 degrees from the dogs' fasting free acid level. Such an occurrence was considered as not being a significant change. In other experiments, the dogs' fasting free acid level was 0 degrees and remained so throughout the procedure. In this last type of result, one can state only that no stimulating effect occurred; obviously, a depressant effect cannot be excluded.

TABLE IV

HEIDENHAIN AND PAVLOV POUCH DOGS—THE EFFECT OF AQUEOUS CAFFEINE CITRATE ON POUCH SECRETIONS

NO.	WEIGHT (LB.)	DOSE OF CAFFEINE (MG.)	ROUTE	EFFECT
117 P	34	150	Subcutaneously	Fasting at 0, and remained 0
20 H	49	300	Subcutaneously	Depression
9 H	42	300	Subcutaneously	Fasting at 0, and remained 0
20 H	49	300	Subcutaneously	Fasting at 0, and remained 0
132 H	45	600	Subcutaneously	Depression
116 P	40	600	Subcutaneously	No significant change

H—Heidenhain pouch dog.

P—Pavlov pouch dog.

In most of these experiments, no significant changes in the volume of the pouch secretions were noted. Aqueous caffeine citrate in dosages of 150, 300, and 600 mg. was injected subcutaneously in six experiments (see Table IV). No stimulation effect on gastric acidity was noted in any instance.

Using comparable dosages of aqueous caffeine alkaloid, somewhat similar results were noted. However, when dosages of 1,200 mg. of aqueous caffeine alkaloid were injected subcutaneously, a stimulation effect of pouch acidity was observed in four of six experiments (66½ per cent). It usually occurred during the third and fourth hour after the administration of the drug. No toxic symptoms were noted in any instance with this dosage. No important differential response in pouch secretions was noted between the Heidenhain (vagus destroyed) and Pavlov (vagus intact) pouch dogs (see Table V A).

TABLE V A

HEIDENHAIN AND PAVLOV POUCH DOGS—THE EFFECT OF AQUEOUS CAFFEINE ALKALOID ON POUCH SECRETIONS

NO.	WEIGHT (LB.)	DOSE (MG.)	ROUTE	EFFECT
11 P	43	300	Subcutaneously	Fasting at 0, and remained at 0
15 P	56	300	Subcutaneously	Stimulation
116 P	40	600	Subcutaneously	No significant change
128 H	42	600	Subcutaneously	Depression
18 P	48	600	Subcutaneously	No significant change
117 P	46	600	Subcutaneously	No significant change
16 P	69	600	Subcutaneously	Fasting at 0, remained 0 throughout
125 P	54	600	Subcutaneously	Fasting at 0, remained 0 throughout
9 H	42	600	Subcutaneously	Depression
129 H	52	600	Subcutaneously	Stimulation
20 H	49	1,200	Subcutaneously	Stimulation
18 P	48	1,200	Subcutaneously	Stimulation
11 P	43	1,200	Subcutaneously	Fasting at 0, remained at 0
20 H	49	1,200	Subcutaneously	Stimulation
132 H	45	1,200	Subcutaneously	Stimulation
132 H	45	1,200	Subcutaneously	Depression

TABLE V B

THE EFFECT OF CAFFEINE ALKALOID IN BEESWAX ON POUCH SECRETIONS

NO.	DOSE (MG.)	ROUTE	EFFECT
44 H	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
16 P	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
20 H	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
11 P	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
254 P*	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation
289 P	2,500	Injected daily for 4 consecutive days intramuscularly	Stimulation

*This experimental animal was subjected to the same experiment on two occasions. In one experiment caffeine sodium benzoate was substituted for the caffeine alkaloid. The results were the same.

Although this dosage of caffeine seems high, it is about one-half of the dosage, calculated on the basis of weight, administered daily (in beeswax) to the cats exhibiting gastric or duodenal ulcers. Computed upon the basis of milligrams per kilogram of average body weight of both cats and pouch dogs used, an equivalent dosage of caffeine in pouch dogs of average weight would be approximately 2,500 mg. In the light of this calculation four Pavlov and two Heidenhain pouch dogs were injected intramuscularly with 2,500 mg. of freshly prepared caffeine alkaloid in beeswax for four consecutive days (see Table V B).

These pouch dogs were injected at 9 A.M. and four one-hour samples of pouch secretions were collected. These samples were titrated for free and total acid as previously described. At 1 P.M. the animals were returned to their cages and given identical diets and water. At 5 P.M. the food pans were removed, although water was allowed up until the test period of the following day. This procedure was repeated on four consecutive days.

In each instance (see Fig. 3) a severe stimulation effect was noted with a marked increase in free acid and volume of the pouch secretions after an initial fall in values. In Dogs 20, 44, and 16, a decrease in the expected response after the third injection of the drug suggests some defect in the preparation injected that day. On the following day, the injections evoked once again the response previously observed. During this four-day test period no symptoms other than mild anorexia and lethargy were noted.

The injections of this same material without caffeine in other pouch dogs evoked no significant secretory response.

Three experiments with two Pavlov pouch dogs were carried out by injecting intramuscularly 2,500 mg. of caffeine alkaloid in beeswax according to the plan previously described. However, daily when the samples were collected, at the peak of the caffeine stimulatory response, atropine sulfate, gr. $\frac{1}{100}$, was injected intramuscularly at a different site. Although the response was somewhat less than anticipated for the following two or three hours, the stimulatory effect of caffeine could not be inhibited. These results are tabulated in Table V B but were not included in Fig. 3.

Roth and Ivy⁹ were unable to demonstrate a gastric secretory response in dogs by the subcutaneous, intramuscular, and intravenous routes with 250 mg. of caffeine sodium benzoate. They observed a stimulatory response in cat and man. These investigators implied that a species difference might be present. Their results are not in accord with our own experimental data. It is true that in the smaller dosages used, no stimulatory response is produced. However, in our experiments, when dogs (on the basis of body weight) were given caffeine in the magnitude of that dosage necessary to produce ulcers in cats, a definite severe stimulatory response of gastric acidity and volume was recorded.

III. *Effect of Caffeine on Gastric Secretion in Man.*—Having established the fact that caffeine does stimulate gastric acidity and is capable of producing ulcers in smaller animals, an attempt was then made to study the effect of caffeine on human gastric acidity. Obviously, to be

of significance, the dosage of caffeine administered had to be in the range of that ingested in everyday activity. Coffee, a universal beverage, was chosen as the test substance. Coffee is known to contain ingredients other than caffeine. These substances are present, however, in minimal amounts. As all the pharmacologic actions of this beverage are essentially those of the alkaloid caffeine, in all probability the effect on gastric secretion can be attributed directly to the caffeine content. The

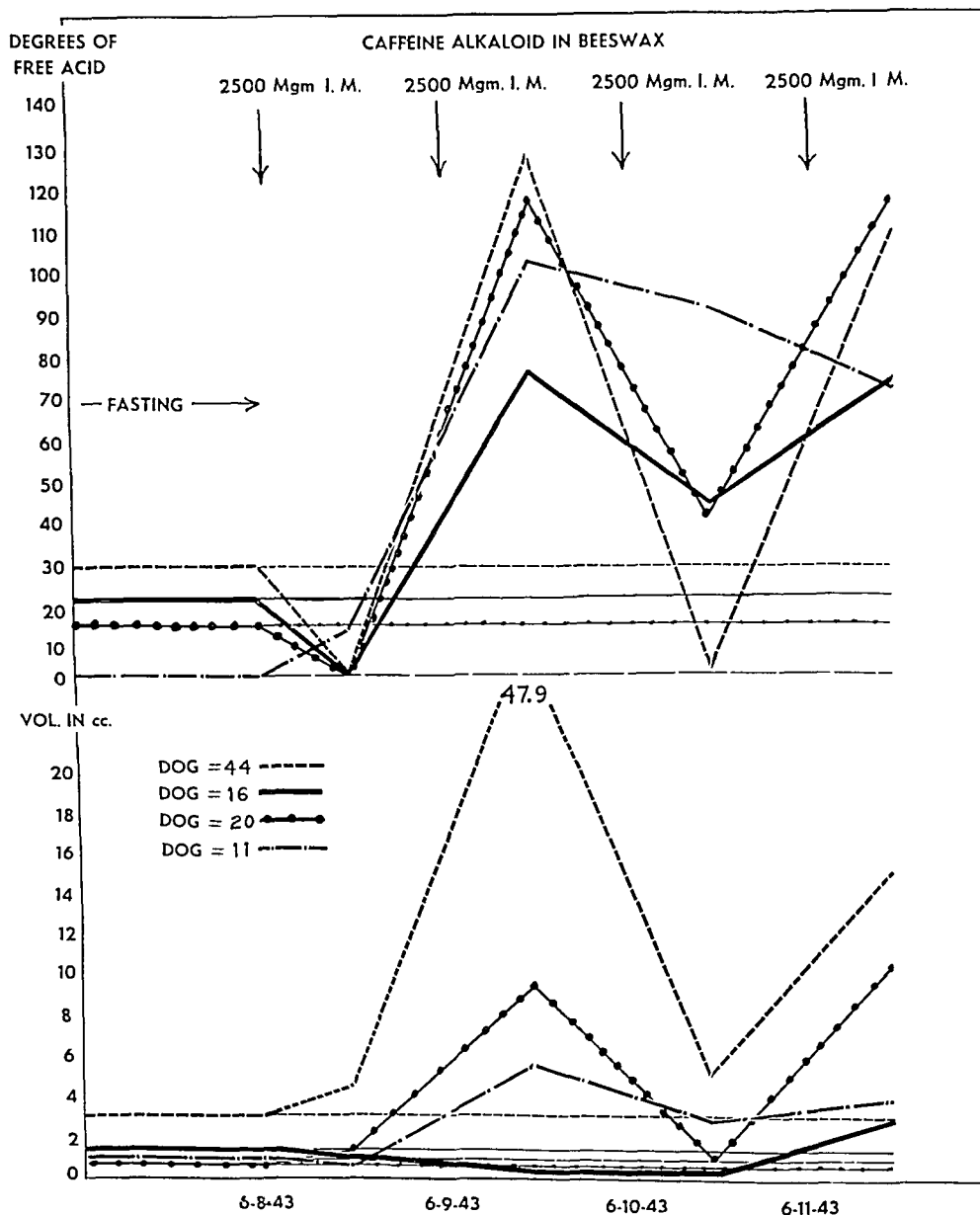


Fig. 3.—Pavlov pouch Dogs 16 and 11, and Heidenhain pouch Dogs 44 and 20. Daily 2500 mg. of caffeine in beeswax were injected intramuscularly for four days. Pouch juice was collected hourly for a four-hour period. This specimen was measured and analyzed for free acid. The points on the graph represent the average free acid and volume per hour of each dog for that particular day.

coffee was used directly from the University Hospital's kitchen at a time when it was being served throughout the hospital.

Patients were chosen at random without reference to age, drinking habits, or primary disease. A light dinner was given the evening before

A total of nineteen such experiments were carried out. In fourteen tests (73.60 per cent) a definite stimulatory effect on gastric acidity and volume was noted.

For convenience these experiments have been grouped into the following categories:

1. Two cups of cold black coffee by mouth.
2. Two cups of hot black coffee by mouth.
3. Two cups of cold black coffee through the nasal tube.
4. Two cups of hot black coffee through the nasal tube (see Figs 4, 5, 6, and 7).

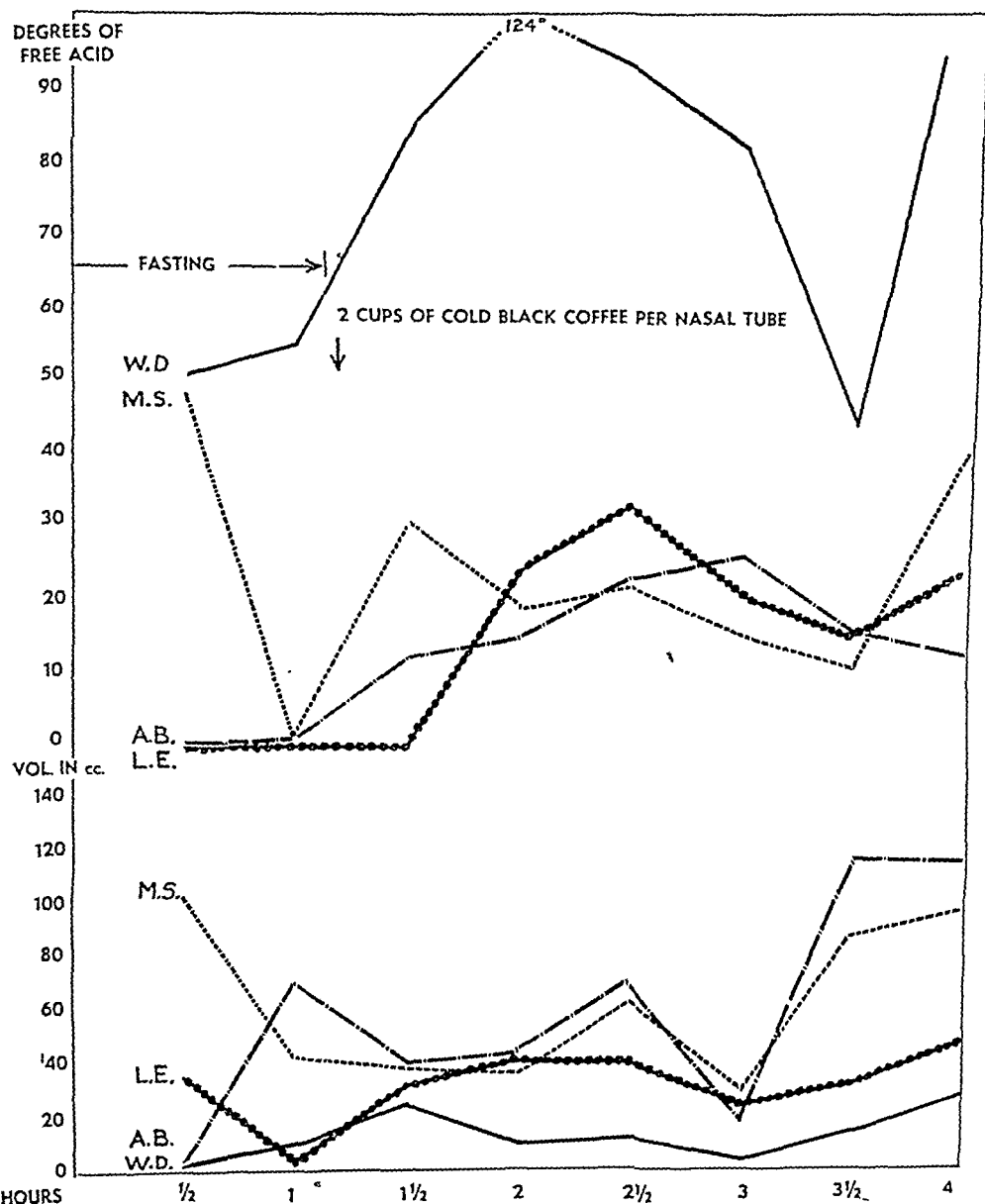


Fig. 6.—In these four patients two cups of cold black coffee were injected into the stomach through the nasal tube. The patients had no knowledge as to the type of material instilled. In three experiments a stimulatory response was evoked. Occasionally a secondary or late stimulation of free acid and volume was observed. This also was noted in other tests.

In each separate category a stimulatory effect was noted in the majority of instances. The severest stimulation effect was observed in those cases in which cold black coffee was given by mouth; these results were approximated by the group of patients receiving cold black coffee by nasal tube. The stimulation of acid with hot black coffee by nasal

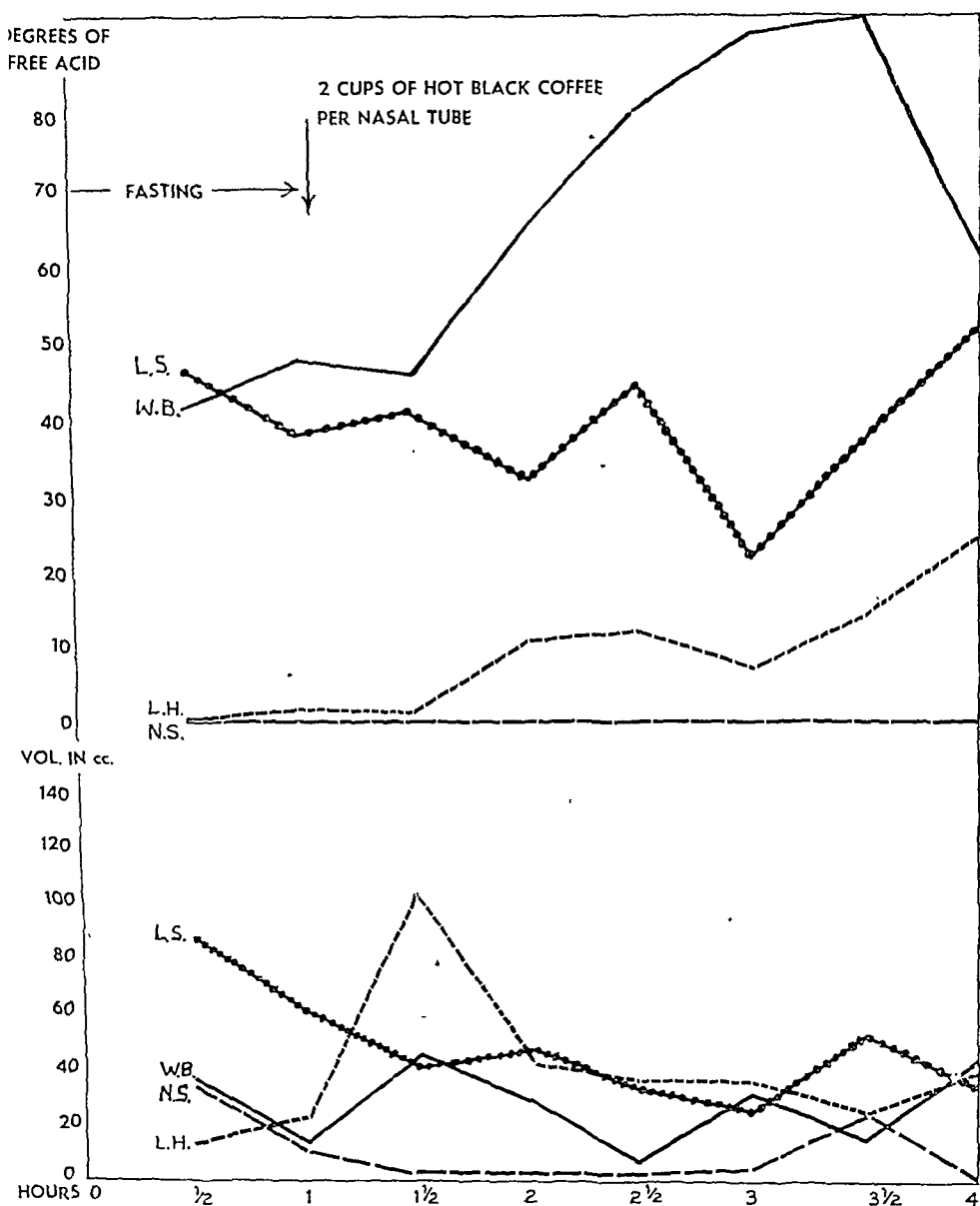


Fig. 7.—Two cups of hot black coffee were instilled by nasal tube into the stomach. Two patients, (L.S. and L.H.) three hours after the injection, began to show a secondary rise in free acid observed previously. One patient (N.S.) revealed no free acid throughout this test. We were unable to establish later his response to histamine. Perhaps this patient was achlorhydric.

tube was not as marked as in those patients allowed the hot coffee by mouth, although large volumes of gastric juice were secreted. In the main however, the stimulation of acid in these groups was not of the same magnitude as the stimulation noted in the groups in which cold coffee was used.

Then, seven patients were tested in the same manner as previously described. In addition to two cups of cold black coffee by mouth, these patients were injected intramuscularly with atropine sulfate, gr. $\frac{1}{75}$. No constant decrease of the stimulatory effect was observed, although there was a temporary decrease in certain instances.

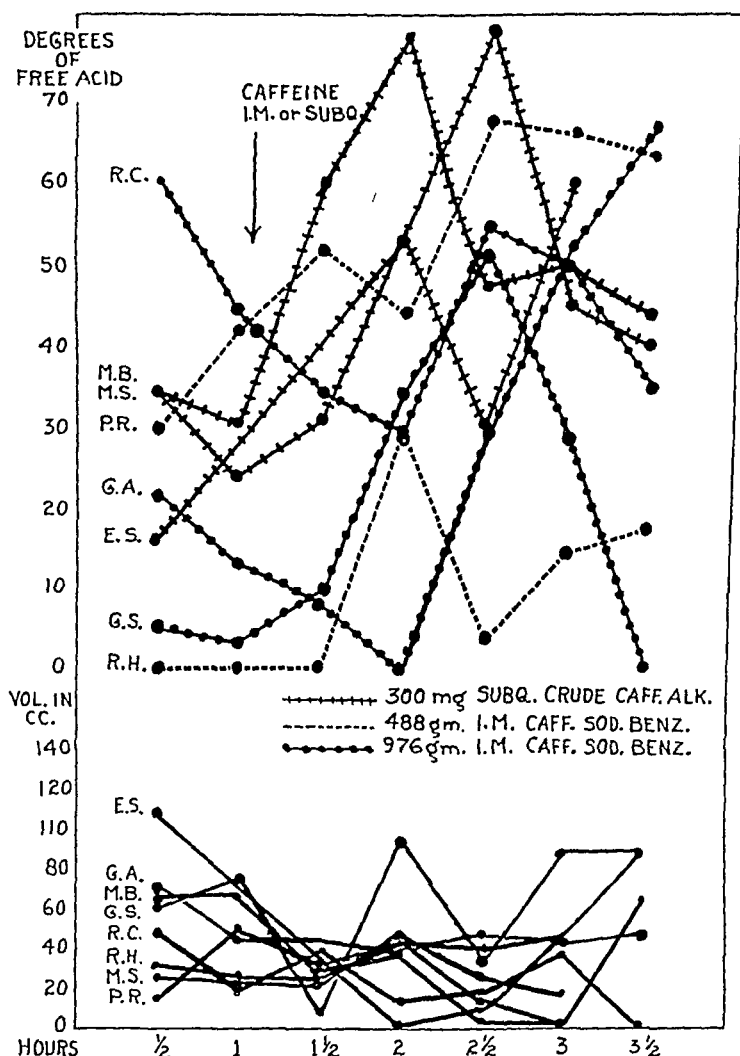


Fig. 8.—These tests were carried out by injecting subcutaneously or intramuscularly aqueous caffeine alkaloid and caffeine sodium benzoate. Both drugs contain 50 per cent caffeine. A moderately severe stimulation of gastric free acid was noted in seven of the eight experiments carried out. The only exception was a patient (R.C.) who had a proved duodenal ulcer. Caffeine sodium benzoate, 976 mg. (gr. 15), intramuscularly produced no stimulation of gastric secretions.

To strengthen further our hypothesis that the stimulatory effect on gastric secretions obtained in human beings with coffee was due to the caffeine present, the following experiments were carried out.

These tests reduplicated in all details the experiments with coffee with two exceptions, namely: (1) that continuous nasal suction was applied throughout (a lapse of one-half hour occurred after coffee was given), and (2) that after the two one-half hour fasting specimens were obtained, synthetic caffeine-containing drugs were injected subcutaneously, intramuscularly, or intravenously.

Fourteen such experiments were performed. Three experiments were unsatisfactory. In one patient's "gastric" samples the material obtained was heavily colored with bile. This suggested that the nasal tube was in the duodenum. Two individuals revealed no free acid throughout the test period with caffeine. Subsequently these patients were tested with histamine. Both were completely achlorhydric. Therefore, these results were discarded.

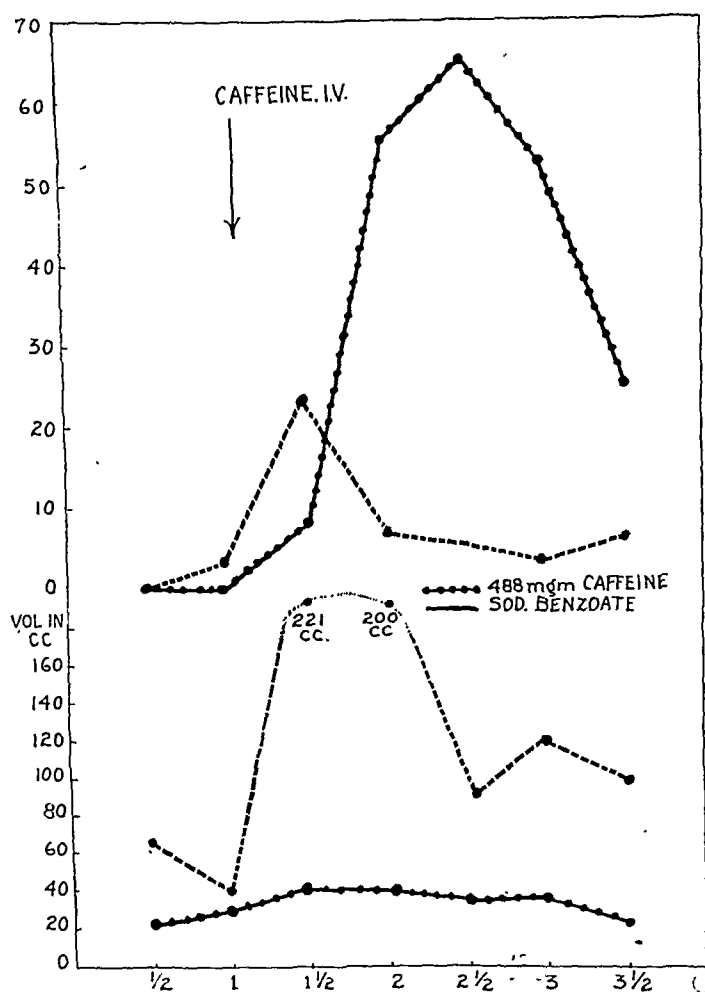


Fig. 9.—Both patients injected with 488 mg. (gr. 7 ss) of caffeine sodium benzoate intravenously revealed a stimulatory response. No untoward reactions were noted.

The eleven experiments considered to be satisfactory can be grouped as follows:

1. Three patients received 300 mg. of aqueous caffeine alkaloid subcutaneously.
2. Five patients received 488 (gr. 7 ss) to 976 mg. (gr. 15) of caffeine sodium benzoate intramuscularly.
3. Two patients received 488 mg. (gr. 7 ss) of caffeine sodium benzoate intravenously.

The crude caffeine alkaloid was dissolved in physiologic saline. One cubic centimeter contained 1 mg. of caffeine alkaloid. This solution was autoclaved by the method used in sterilizing all parenteral fluids in this hospital. This was administered as a hypodermoclysis into the thigh.

The caffeine sodium benzoate injected intramuscularly was prepared on the wards in the usual manner. This was administered into the deltoid muscle by means of an intramuscular needle. The intravenously administered caffeine sodium benzoate was dissolved in 10 c.c. of saline solution and injected into the antecubital vein.

Aqueous caffeine alkaloid and caffeine sodium benzoate contain 50 per cent of caffeine. Therefore, the actual amount of caffeine injected is one-half of the total dosage of the caffeine sodium benzoate or caffeine alkaloid administered.

In nine of the ten experiments performed (90 per cent), a definite stimulation of the gastric acidity was produced (see Figs. 8 and 9). There was occasionally a marked increase in the volume of gastric juice. This was the exception rather than the rule. In general, there was a slight to moderate increase in the volume of gastric juice secreted during the test period. In one instance, 996 mg. (gr. 15) of caffeine sodium benzoate injected intramuscularly evoked no stimulatory response. This occurred in a 30-year-old patient (R. C.) who had a proved duodenal ulcer. Although the usual response was not noted, this patient complained of epigastric pain. No significant side effects were noted in the other patients.

SUMMARY

When 200 mg. of crude caffeine alkaloid in beeswax were injected daily intramuscularly in a series of five guinea pigs, the toxic manifestations were so severe that death ensued too rapidly for any satisfactory data to be obtained. However, in a series of ten guinea pigs in which the dosage was reduced to 100 mg. of caffeine alkaloid in beeswax injected in a similar fashion, eight (80 per cent) guinea pigs developed some degree of upper gastroduodenal pathology. Four (40 per cent) exhibited "peptic" erosions or ulcers. Microscopically, these are typical ulcers similar to those found in man superimposed on a moderate to severe gastritis.

Cats receiving intramuscularly 300 mg. of caffeine alkaloid in beeswax daily exhibited upper gastrointestinal pathology in fourteen of twenty-six animals. Eleven of these cats (40 per cent) developed "peptic" erosions and/or definite ulcers.

In standardized pouch dogs, the subcutaneous injection of aqueous caffeine citrate and aqueous caffeine alkaloid in dosages up to 600 mg. produced no significant change in pouch acidity and volume. However, when the dosage of caffeine alkaloid was increased to 1,200 mg. a definite stimulation effect of pouch acidity and volume was observed.

This dosage in dogs was computed to be approximately one-half of the dosage used to produce ulcers in cats on the basis of milligram per kilograms of body weight. Consequently, four pouch dogs were injected with 2,500 mg. of caffeine alkaloid in beeswax intramuscularly for four consecutive days. A marked increase of pouch acidity and volume occurred.

These latter results suggest that the ulcers produced in cats by the injection of caffeine alkaloid in beeswax may well be explained on the basis of the stimulation of free acid.

Nineteen experiments were conducted on human beings. To evaluate the effect of coffee on gastric acidity and volume, these tests were devised to control the possible thermal and psychic effects of the coffee. The ingestion of cold coffee produced the most striking results. It is possible that the increased temperature of the hot beverage inhibited to some degree the gastric secretory response. Psychic stimulation appeared to be of no real significance. In eleven instances (73 per cent) a definite stimulatory effect on gastric acidity was observed. The variation in the volume of gastric juice was not striking.

In nine of ten experiments (90 per cent) in man, a striking stimulatory response of gastric acidity was observed when caffeine-containing drugs were administered parenterally (aqueous caffeine alkaloid, 300 mg. and caffeine sodium benzoate, 488 to 976 mg.).

Computed on the basis of milligram per kilogram of body weight, the dosage of aqueous caffeine alkaloid or caffeine sodium benzoate necessary to produce a stimulation of gastric acidity in man is approximately 4.3 mg. per kilogram of body weight. In guinea pigs plus-minus 200 mg. of crude caffeine alkaloid (in beeswax) per kilogram produced ulcers; in cats approximately 104.8 mg. of the same material per kilogram were necessary for ulcer formation. In pouch dogs (average weight 20 kilograms) a total dose of 1,200 mg. of aqueous caffeine alkaloid was needed to evoke a stimulation of gastric secretions in the majority of experiments. This is approximately 60 mg. of drug per kilogram. This dosage is twelve times the amount which regularly produces a moderately severe stimulation of gastric acidity in man. It is apparent that man's gastric secretory mechanism is exceedingly sensitive to caffeine stimulation. It is undoubtedly much more sensitive to the caffeine effect than is that of the dog. Further comparisons of dosage on the basis of body weight suggest also that man's gastric secretory apparatus is probably more sensitive to caffeine than both the guinea pig and the cat.

No important differential response in pouch secretion was observed in any experiments between the Heidenhain (vagus destroyed) and Pavlov (vagus intact) pouch dogs. The fact that a stimulatory effect was noted in the Heidenhain pouch dogs suggests that the vagus nerve is not necessary for the production of this effect. However, in Pavlov pouch dogs and in human beings, atropine sulfate seems to produce a minimal temporary depression in pouch and gastric secretions in certain instances. Therefore, the stimulatory effect of caffeine must occur mainly by direct action on the parietal cells of the stomach.

CONCLUSIONS

1. Typical "peptic" ulcers were produced in 40 per cent of guinea pigs and cats by the daily intramuscular injections of caffeine alkaloid in beeswax.

2. The subcutaneous injection of 1,200 mg. of aqueous caffeine alkaloid in pouch dogs caused a stimulation effect of pouch acidity and volume in 66 $\frac{2}{3}$ per cent of the experiments. Similarly injected smaller doses of aqueous caffeine citrate and caffeine alkaloid produced no stimulation effect.

3. Pouch dogs injected with 2,500 mg. of caffeine alkaloid in beeswax for four consecutive days exhibited a marked and prolonged increase

of free acidity and volume of the pouch secretions. This dosage in dogs was equivalent to the dosage used to produce ulcers in cats. This suggests that the mechanism of ulcer production with caffeine is related to the increased production of free acid.

4. In 73 per cent of the human beings tested, two cups of black coffee caused a definite stimulatory effect on gastric acidity and volume. In all probability this can be attributed to the caffeine content of the coffee.

5. In 90 per cent of the human beings tested, aqueous caffeine alkaloid and caffeine sodium benzoate in 300 to 976 mg. doses evoked a moderately severe stimulation of gastric acidity and to a lesser degree volume, when administered subcutaneously, intramuscularly, or intravenously.

6. The gastric secretory mechanism in man is very sensitive to caffeine stimulation, much more so than that of the dog, and possibly the guinea pig and cat.

7. The stimulation effect observed with caffeine on the gastric and pouch secretions in man and dogs is mediated mainly through direct action on the parietal cells of the stomach. The effect of caffeine on gastric secretions apparently is not mediated through the vagus nerves.

8. These results suggest that the use of caffeine-containing beverages is contraindicated in the ulcer patient.

REFERENCES

1. Allard, E.: Ueber Theocoinvergiftung, *Deutsches Arch. f. klin. Med.* 80: 510, 1901.
2. Code, C. F., and Varco, R. L.: Chronic Histamine Action, *Proc. Soc. Exper. Biol. & Med.* 44: 475, 1940.
3. Hanke, H.: Zur Pathogenese Der Experimentellen akuten und Erosiven Gastritis Infolge Parenteraler Zufuhr Bestimmter Pharmaca (Morphin, Pilocarpin, Coffein), *Klin. Wehnschr.* 12: 1524, 1933.
4. Hanke, H.: Experimentelle Erzeugung Chronischer Magengeschwüre Durch Coffein, *Klin. Wehnschr.* 13: 978, 1934.
5. Hanke, H.: Zur Pathogenese der akuten erosiven Gastritis: Die Experimentelle Hämatogene Coffein Gastritis, *Arch. f. klin. Chir.* 178: 607, 1934.
6. Judd, E. S.: Experimental Production of Peptic Ulcers With Caffeine, Interdepartmental Seminar, University of Minnesota, April, 1942; Abstracted in *Bull. Am. Coll. Surgeons* 28: 46, 1943.
7. Molteni, M.: Lesioni Gastriche da Caffaina; Experimental Study, *Arch. ital. di chir.* 53: 135, 1938.
8. Pincussohn, L.: Die Wirkung des Koffees und des Kakaos auf die Magensaftsekretion, *München. med. Wehnschr.* 53: 1248, 1906.
9. Roth, J. A., and Ivy, A. C.: The Effect of Caffeine Upon Gastric Secretion in the Dog, Cat and Man, *Am. J. Physiol.* 141: 454, 1944.
10. Roth, J. A., Ivy, A. C., and Atkinson, A. J.: Caffeine and "Peptic" Ulcer. Relation of Caffeine and Caffeine Containing Beverages to the Pathogenesis. Diagnosis and Management of "Peptic" Ulcer, *J. A. M. A.* 126: 814, 1944.
11. Salant, W., and Rieger, J. B.: The Toxicity of Caffeine, *J. Pharmacol. & Exper. Therap.* 1: 572, 1909.
12. Sollmann, T.: *A Manual of Pharmacology*, Ed. 5, Philadelphia and London, 1936, W. B. Saunders Company.

THE PEDICLED JEJUNAL TRANSPLANT ONTO THE GASTRIC WALL

EVALUATION OF ITS EFFECT UPON GASTRIC ACIDITY AND FAILURE OF SUCH
TRANSPLANTS TO AFFORD PROTECTION AGAINST ULCER PROVOKED
BY HISTAMINE IN BEESWAX

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ANDRUS and his associates have devised a surgical technique which, according to their observations, proved valuable in the treatment of experimentally produced ulcer in the dog as well as in the surgical management of spontaneously occurring acid-peptic ulcer of man. The operation consists of creating a defect in the gastric wall and implanting into it a short segment of jejunum, pedicled on its own blood supply. This transplant functions as a mucosal graft. The continuity of the jejunum is re-established by end-to-end anastomosis.

In experimental studies on dogs, Andrus and his associates¹⁻⁷ report that the jejunal graft caused a reduction in gastric acidity and an elevation of the pH of the gastric wall. The effects of the potent secretagogues, histamine and alcohol, were nullified they observed, and in some instances even reversed. The experimental production of peptic ulcer by the histamine and beeswax method was prevented, and on one occasion previously induced duodenal erosions healed in the face of continued postoperative stimulation. Quantitative studies showed an actual reduction of acid production of the parietal cells of the stomach and a slight increase in nonparietal secretion.

These investigators studied the mode of action of the implanted jejunal graft by instilling jejunal washings, obtained through a Thiry fistula, into the stomachs of dogs. The resulting diminution of acid secretion following histamine stimulation, they concluded, indicated the presence of an acid-controlling agent in the jejunum. Pedicled grafts which were taken from the jejunum proved to be more effective in influencing gastric acid secretion than duodenal grafts, which had only a slight effect; ileal and colonic segments were valueless. Gastrojejunos-tomy in dogs, they found, failed to influence gastric secretion, whereas the conversion of the parastomal mucosa into a pedicled graft caused a typical reduction in acidity.

In the clinical application of the jejunal graft operation, they observed reduction of hyperacidity in three out of a total of four patients. The fourth patient showed clinical improvement with no concomitant change in acid secretion.

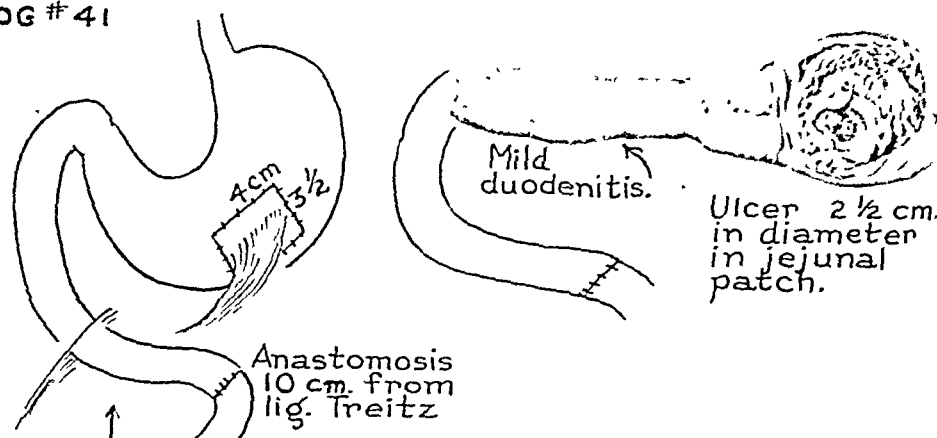
The researches presented here were supported by grants of the Citizens' Aid Society, the Augustus L. Searle and the Graduate School of the University of Minnesota.

*Fellow of the National Cancer Institute, Bethesda, Md.

†Fellow from one of the American Republics working at University of Minnesota Hospitals through the Inter-American Student and Professor Exchange at Washington, D. C.

Fig. 1

SERIES 1
DOG #41



PROCEDURE 11-9-43

AUTOPSY 2-16-44

DAILY INJ. 30 MG. HIST IN
BEESWAX STARTED 1-3-44

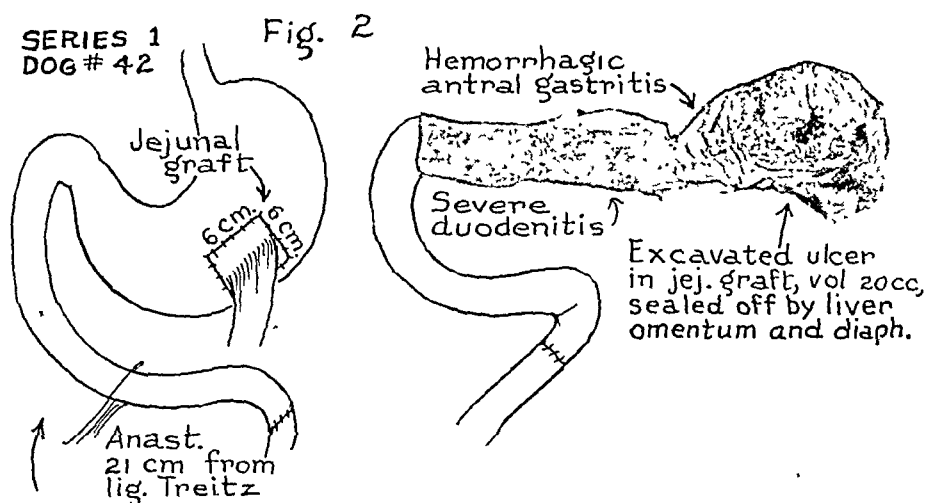
EXPERIMENT 1

Series 1, Dog 41. Mongrel male, weight 36 pounds (Fig. 1)

10/22/43 Distemper vaccine given
11/ 9/43 Jejunal graft operation
1/ 3/44 Daily injections 30 mg. of histamine in beeswax started
2/16/44 Weight 31 pounds, lost 5 pounds, general condition fair, sacrificed

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	9.5	4.49	16.13	4.51
	1/2	24.5	118.08	128.44	1.54
	1	5.4	8.17	16.34	3.32
	1 1/2	5.3	0	6.46	6.41
	2	11.0	2.04	16.34	6.54
12/15/43	Fasting	44.0	0	12.25	6.9
	1/2	51.5	60.85	72.90	1.36
	1	16.0	62.49	77.80	1.44
	1 1/2	7.0	21.03	49.01	1.64
	2	11.0	2.04	10.41	6.18
12/17/43	Fasting	33.0	1.6	11.6	7.19
	1/2	29.0	71.5	82.7	1.23
	1	17.0	51.1	91.3	1.44
	1 1/2	4.7	0	11.0	7.28
	2	24.0	0	5.9	7.30
12/21/43	Fasting	0.8	0	24.25	8.55
	1/2	49.0	85.76	100.06	1.58
	1	24.0	43.09	67.18	1.50
	1 1/2	15.0	1.84	24.10	4.05
	2	3.8	8.75	30.93	2.14



PROCEDURE 11-10-43

AUTOPSY 2-16-44

DAILY INJ 30 MG HIST. IN
BEESWAX STARTED 1-3-44

EXPERIMENT 2

Series 1, Dog #2. Mongrel male, weight 50 pounds (Fig. 2)

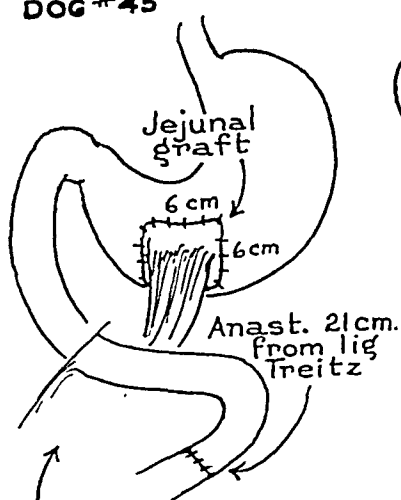
11/10/43 Jejunal graft operation
1/ 3/44 Daily injection of 30 mg. histamine in beeswax started
2/16/44 Weight 40 pounds, dog ill, lost 10 pounds, sacrificed, autopsy

Results of Gastric Analyses

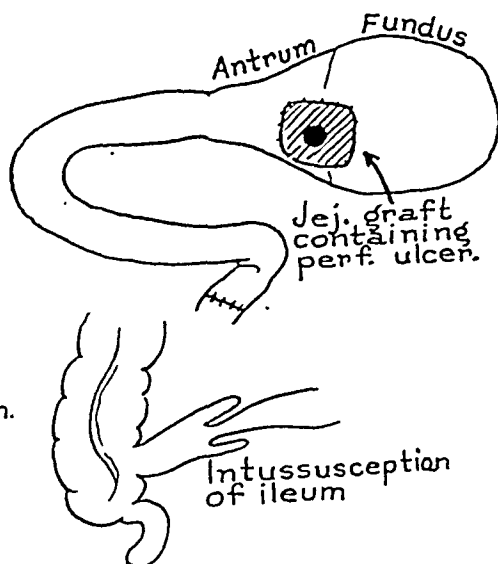
DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	15.0	14.09	36.55	1.76
	½	14.0	61.26	75.15	1.58
	1	51.0	89.03	102.10	1.55
	1½	5.8	2.04	6.13	5.30
	2	23.5	30.22	44.72	1.67
12/15/43	Fasting	5.5	1.84	7.96	6.56
	½	50.0	83.52	95.97	1.34
	1	40.5	73.51	79.03	1.50
	1½	9.0	0	4.7	6.96
	2	3.1	0	4.08	7.46
12/17/43	Fasting	1.2	0	9.2	8.34
	½	30.0	38.8	52.5	1.51
	1	42.0	79.6	91.9	1.39
	1½	17.0	1.42	6.1	6.29
	2	1.1	0	9.2	8.01
12/23/43	Fasting	7.0	0	12.46	8.06
	½	32.0	77.60	91.07	1.53
	1	25.0	73.10	83.72	1.46
	1½	4.1	1.27	5.11	7.10
	2	13.0	0.82	11.23	7.14
12/30/43	Fasting	7.0	1.84	7.76	5.73
	½	101.5	85.56	117.42	1.18
	1	75.0	103.11	115.99	1.27
	1½	9.5	0	19.20	6.99
	2	2.8	0	20.42	7.67

SERIES 1
DOG #45

Fig. 3



PROCEDURE 11-15-43
DAILY INJ. 30MG HIST. IN
BEESWAX STARTED 1-3-44



AUTOPSY 1-23-44

EXPERIMENT 3

Series 1, Dog 45. Mongrel male, weight 45 pounds (Fig. 3)

11/15/43 Jejunal graft operation
1/3/44 Daily injections of 30 mg. of histamine in beeswax started
1/23/44 Expired, autopsy

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	6.2	10.21	24.71	3.40
	1/2	15.0	98.02	109.86	1.49
	1	53.5	113.13	120.27	1.28
	1 1/2	32.0	67.39	77.60	1.38
	2	25.5	48.60	59.01	1.61
12/15/43	Fasting	13.0	1.02	14.29	6.54
	1/2	63.0	93.93	102.51	1.46
	1	43.0	89.85	100.06	1.54
	1 1/2	17.0	63.30	77.60	1.41
	2	8.0	0	8.17	6.56
12/21/43	Fasting	6.6	0	20.42	7.02
	1/2	25.5	36.76	59.01	1.70
	1	3.7	0	20.42	7.11
	1 1/2	17.0	0	26.55	6.73
	2	5.1	0	27.57	7.85
12/23/43	Fasting	1.1	0	10.22	5.66
	1/2	34.0	59.42	71.47	1.46
	1	32.0	59.22	72.70	1.47
	1 1/2	4.5	1.13	6.80	6.93
	2	17.0	1.02	10.21	7.64

THIS STUDY

The interesting findings reported by Andrus and his associates suggested that this observed novel effect of a small jejunal pedicled graft on gastric acid secretion should be studied further. Our studies have been limited to an investigation of the effect of the pedicled jejunal graft on gastric secretion in dogs.

Method.—Preparation of the dogs for surgery consisted of deworming them with Nema capsules and placing them in individual cages. Their diet was composed of table scraps with a daily supplement of prepared dog food, 200 Gm. of horse meat, six tablets of brewers' yeast, and 50 mg. of cevitamic acid.

EXPERIMENT 4

Series 1, Dog. 93. Mongrel female, weight 28 pounds (Fig. 4)

1/19/44	Dewormed
3/ 8/44	Jejunal graft operation
5/30/44	Daily injection of 30 mg. histamine in beeswax started
6/25/44	Expired, autopsy

Results of Gastric Analyses

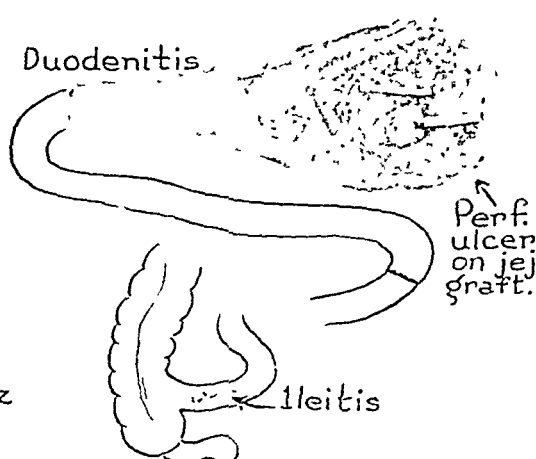
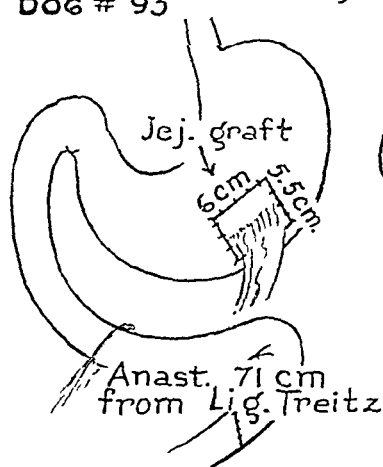
DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
1/21/44	Fasting	16.5	0	10.97	5.23
	½	72.0	105.48	117.37	1.17
	1	10.1	2.08	18.34	5.59
	1½	0.7	20.84	31.26	2.53
	2	1.7	2.78	9.03	5.83
1/24/44	Fasting	0.05	0	20.0	Too small
	½	83.0	79.4	87.53	1.26
	1	2.4	5.0	19.0	3.65
	1½	2.9	3.6	20.0	3.73
	2	2.3	0	9.0	7.14
4/ 3/44	Fasting	9.7	0	10.42	6.46
	½	30.0	87.53	95.03	1.63
	1	8.3	31.47	47.52	1.98
	1½	4.8	2.08	9.12	7.03
	2	3.8	0	12.16	8.23
4/10/44	Fasting	13.0	0	8.34	6.60
	½	12.5	53.31	66.27	1.54
	1	13.5	25.22	40.01	1.95
	1½	6.3	0	6.25	7.62
	2	3.8	0	5.76	7.48
4/17/44	Fasting	17.0	0	7.29	7.43
	½	25.5	55.23	64.40	1.57
	1	0.1	52.10	93.78	Too small
	1½	10.0	2.29	10.84	6.54
	2	6.2	0	7.29	7.31
4/24/44	Fasting	5.2	0	12.30	7.54
	½	15.0	65.23	83.99	1.42
	1	1.5	41.68	76.38	1.85
	1½	7.5	0	10.42	6.54
	2	11.5	0	17.09	6.59
5/18/44	Fasting	3.1	7.0	39.27	2.41
	½	32.5	68.62	83.01	1.60
	1	45.0	66.68	76.21	1.55
	1½	3.0	0	14.58	6.86
	2	8.5	0	12.44	6.53
5/23/44	Fasting	0.32	0	16.23	Too small
	½	25.0	56.18	66.10	1.46
	1	40.0	91.56	101.48	1.34
	1½	17.0	62.21	71.73	1.43
	2				

Under strict aseptic surgical technique, the jejunal transplant to the stomach wall was carried out in precisely the same manner as described by Andrus. The size of the graft and the position from which it was taken in the small intestine will be described in the individual protocols.

All gastric analyses were made with the animal in a fasting condition, and without the use of anesthesia. The fasting gastric contents were obtained by means of a stomach tube, after which 0.5 mg. of histamine base was administered subcutaneously, and an aspiration was done every thirty minutes during the succeeding two hours. The volume was measured and the free and total HCl and pI were determined.

SERIES 1
DOG # 93

Fig. 4



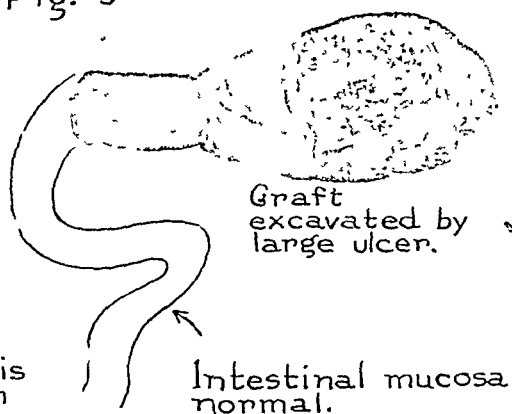
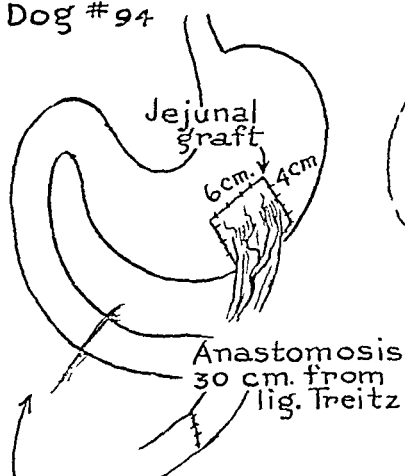
PROCEDURE 3-8-44

DAILY INJ. OF HIST. IN
BEESWAX STARTED 5-30-34

AUTOPSY 6-25-44

SERIES 1
Dog #94

Fig. 5



PROCEDURE 3-9-44
Daily inj. 30 mg. Hist. in
beeswax started 5-30-44

AUTOPSY 7-17-44

THE EXPERIMENTS

Three series of experiments were completed on a total of thirteen dogs.

Series 1.—The first series of experiments was carried out on a group of ten dogs. Seven were subjected to the jejunal graft operation (Dogs 41, 42, 45, 93, 94, 95, and 96) and three control dogs (Dogs 58, 59, and 60) were not operated upon. Gastric analyses were made on Dogs 58, 59, and 60, postoperatively only on Dogs 41, 42, and 45, and both preoperatively and postoperatively on Dogs 93, 94, 95, and 96. Eight dogs were subjected to continuous gastric hypersecretion by daily intramuscular implantation of histamine in beeswax (Dogs 41, 42, 45, 58, 59, 60, 93, and 94). Dog 95 succumbed after a subtotal gastric pouch operation. A Heidenhain gastric pouch containing the pedicled jejunal graft was made in Dog 96.

EXPERIMENT 5

Series 1, Dog 94. Mongrel female, weight 20 pounds (Fig. 5)

3/ 9/44 Jejunal graft operation
 5/23/44 Triple histamine test
 5/30/44 Daily injections of 30 mg. histamine in beeswax started
 7/17/44 Sacrificed, autopsy, tolerated histamine very well

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	PH
1/19/44	Fasting	2.7	0	11.46	7.5
	½	15.1	44.18	60.44	1.54
	1	4.0	8.34	26.05	2.26
	1½		No sample		
	2		No sample		
1/21/44	Fasting	0.6	0	17.37	Too small
	½	42.5	95.86	102.53	1.28
	1	0.9	10.42	23.15	Too small
	1½	3.5	0	17.37	4.37
	2	1.82	6.51	35.17	Too small
4/ 3/44	Fasting	5.7	0	7.64	7.53
	½	20.5	56.06	66.69	1.78
	1	30.0	49.60	60.02	1.97
	1½	3.3	3.75	14.59	5.73
	2		No sample		
4/10/44	Fasting	7.3	0	10.42	7.05
	½	5.0	74.82	80.86	1.53
	1	17.6	6.25	16.67	1.44
	1½	2.0	0	6.25	7.23
	2	7.9	0	8.96	7.19
4/17/44	Fasting	7.0	27.09	43.56	1.83
	½	30.0	91.70	100.87	1.46
	1	4.3	2.64	7.55	6.56
	1½	4.9	1.16	4.63	6.85
	2	3.5	0	5.21	7.41
5/18/44	Fasting	6.0	0	5.83	6.92
	½	17.5	50.44	69.6	1.62
	1	30.0	80.87	95.26	1.52
	1½	18.0	34.21	56.18	1.65
	2	1.9	0	7.12	7.01
5/23/44	Fasting	15.0	30.13	44.52	1.63
	½	72.0	52.88	67.07	1.50
	1	42.0	65.90	75.62	1.50
	1½	37.0	71.93	81.07	1.46

EXPERIMENT 6

Series 1, Dog 95. Mongrel male, weight 25 pounds

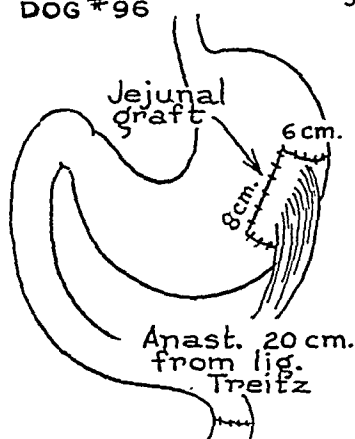
- 2/24/44 Jejunal graft operation, graft 6 by 6 cm., taken 23 cm. from ligament of Treitz, placed on anterior surface of middle third of stomach
- 5/ 8/44 Subtotal gastric pouch; dog expired due to shock, autopsy

Results of Gastric Analyses

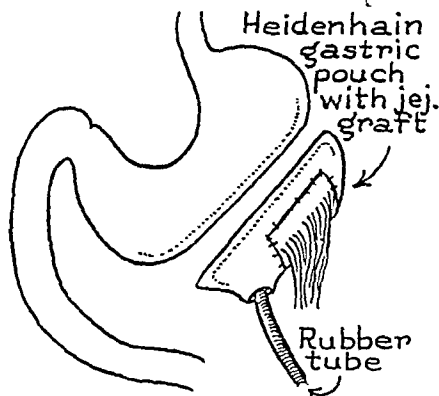
DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
1/19/44	Fasting	9.5	0	23.13	3.21
	½	48.2	112.33	120.68	1.00
	1	20.4	120.84	129.21	0.88
	1½	1.4	0	19.35	Too small
	2	0.2	0	41.68	Too small
1/21/44	Fasting	1.32	0	20.84	3.96
	½	97.3	106.28	116.02	1.26
	1	36.9	101.91	116.29	1.17
	1½	12.9	41.68	72.94	1.39
	2	5.0	3.13	56.27	1.53
1/24/44	Fasting	0.03	0	100.0	Too small
	½	65.0	100.03	114.2	1.28
	1	134.0	15.0	41.68	1.65
	1½	1.1	28.0	41.0	Too small
	2	0.65	5.0	23.3	Too small
4/ 3/44	Fasting	19.0	0	9.76	6.54
	½	55.0	76.90	89.40	1.55
	1	32.5	91.70	97.95	1.72
	1½	1.0	5.21	28.13	5.93
4/10/44	Fasting	5.1	0	15.0	7.30
	½	17.5	24.80	41.89	2.05
	1	24.6	20.84	39.60	2.14
	1½	8.7	0	12.5	6.65
4/17/44	Fasting	8.5	0	6.25	7.21
	½	60.5	87.32	96.07	1.33
	1	18.5	44.81	58.4	1.62
	1½	1.6	0	6.25	8.10
	2	0.8	0	13.03	Too small

SERIES 1
DOG #96

Fig. 6



PROCEDURE 2-22-44



PROCEDURE 5-28-44

EXPERIMENT 7

Series 1, Dog 96. Mongrel male, weight 36 pounds (Fig. 6)

2/22/44	Jejunal graft operation
5/28/44	Heidenhain pouch operation including jejunal graft
6/19/44	Gastric pouch analysis
6/20/44	Twenty-four-hour gastric pouch analysis
6/26/44	Twenty-four-hour gastric pouch analysis
7/ 5/44	Gastric pouch analysis
7/ 7/44	Gastric pouch analysis

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
1/19/44	Fasting	10.1	10.21	81.07	2.11
	½	80.1	66.48	97.95	1.28
	1	20.1	47.51	81.28	1.35
	1½	4.1	17.56	47.33	2.85
	2	No sample			
1/21/44	Fasting	1.69	0	10.42	6.44
	½	43.0	66.69	82.94	1.32
	1	20.0	24.80	50.02	1.60
	1½	21.9	42.70	68.69	1.37
	2	20.9	62.50	78.15	1.30
4/ 3/44	Fasting	4.7	0	10.16	6.97
	½	17.5	74.61	83.57	1.98
	1	3.1	3.75	12.09	3.40
	1½	1.3	0	20.84	6.61
	2	0.9	0	72.94	Too small
4/10/44	Fasting	11.0	0	6.46	7.38
	½	29.5	67.73	82.94	1.40
	1	24.5	22.92	39.60	1.96
	1½	0.35	0	59.40	Too small
	2	3.5	0	71.45	8.08
4/17/44	Fasting	23.0	2.50	10.21	3.55
	½	35.5	83.36	92.53	1.76
	1	3.2	0.70	6.95	2.14
	1½	3.7	0	5.95	7.25
	2	5.1	0	5.21	7.88
5/18/44	Fasting	6.0	0	6.8	7.31
	½	35.5	55.02	64.15	1.70
	1	5.5	0	7.0	7.46
	1½	9.0	0	7.39	7.33
	2	3.7	0	9.36	7.56
5/23/44	Fasting	1.1	18.47	25.22	Too small
	½	15.0	33.05	40.24	1.73
	1	1.6	0	10.30	7.99
	1½	30.0	66.1	71.54	1.37

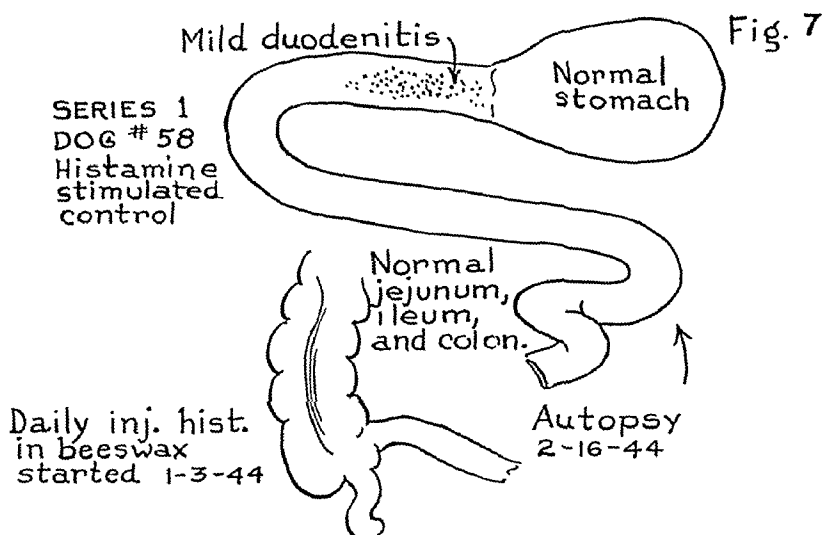
Results of Gastric Pouch Analyses

6/19/44	Sample 1	3.2	0	43.04	4.06
Stimulus:	Sample 2	0.6	0	32.28	Too small
0.5 mg.	1 N	31.0	109.75	123.09	1.09
histamine	2 N	4.6	96.30	103.83	1.25
subcuta- neously	3 N	1.5	38.74	55.05	2.20

EXPERIMENT 7—CONT'D

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
6/20/44	Sample 1	1.4	68.40	93.00	1.73
Stimulus:	Sample 2	1.0	44.12	87.16	Too small
30 mg.	1 N	29.0	112.12	125.03	0.95
histamine	2 N	47.0	124.60	137.48	0.89
in bees-	3 N	49.0	122.02	128.26	0.99
wax	4 N	32.0	117.28	124.39	0.89
intramus-	5 N	4.83	115.99	122.23	0.96
cularly	6 N	16.0	120.51	129.55	1.07
	7 N	22.0	120.51	126.97	1.00
	8 N	18.6	107.17	112.23	1.04
	9 N	12.0	90.17	98.13	1.04
	10 N	15.0	113.63	119.87	0.94
	11 N	21.0	78.76	90.38	1.10
	12 N	9.0	25.82	38.52	1.57
	13 N	13.0	32.01	42.82	1.51
	14 N	18.0	77.90	90.38	1.23
	15 N*	23.0	44.98	122.66	1.40
	16 N*	17.0	69.29	118.79	1.24
	17 N*	26.5	79.62	114.49	1.20
	18 N	4.0	61.33	114.78	1.25
	19 N	5.0	0	51.11	2.95
	20 N	21.0	78.12	93.61	1.20
	21 N	14.0	73.17	81.56	1.17
	22 N	8.0	74.89	81.56	1.20
	Mixed samples				1.26
6/27/44	Sample 1	4.4	0	15.87	3.77
Stimulus:	Sample 2	2.4	0	32.08	7.20
30 mg.	1 N	33.0	121.59	141.82	0.94
histamine	2 N	45.0	140.31	161.18	0.99
in bees-	3 N	50.8	135.15	144.18	0.96
wax	4 N	46.5	131.27	140.1	0.89
intramus-	5 N	43.0	123.09	134.5	1.13
cularly	6 N	26.8	118.21	126.75	0.95
	7 N	20.3	109.32	108.14	1.03
	8 N	15.0	109.97	122.09	0.96
	9 N	10.0	109.54	123.09	0.99
	10 N	12.0	109.75	123.96	0.96
	11 N	5.2	98.99	118.58	1.09
	12 N	7.5	94.26	115.56	1.03
	13 N	7.8	68.86	125.89	1.17
	14 N*	1.8			3.66
	15 N*	2.0			4.00
	16 N*	2.8			4.74
	17 N*	2.7			4.66
	18 N*	1.6	Samples too bloody to do free and total acid determination		4.30
	19 N*	1.2			4.12
	20 N*	5.3			4.85
	21 N*	1.6			3.65
	22 N*	9.0			1.28
	23 N	No sample			
	24 N	No sample			
7/ 5/44	Sample 1	4.8	0	27.76	5.97
Stimulus:	Sample 2	2.6	0	29.05	5.00
0.5 mg.	1 N	28.0	94.90	112.12	1.17
histamine	2 N	3.8	20.33	59.70	1.80
subcuta-	3 N	1.0	0	59.18	Too small
neously					
7/ 7/44	Sample 1	3.6	0	53.75	2.95
Stimulus:	Sample 2	0.42	0	74.24	Too small
0.5 mg.	1 N	20.0	92.54	118.82	1.15
histamine	2 N	2.9	32.28	59.83	1.52
subcuta-	3 N	2.1	0	45.19	3.51
neously					

*Bloody samples.



EXPERIMENT 8

Series 1, Dog 58, Control dog.

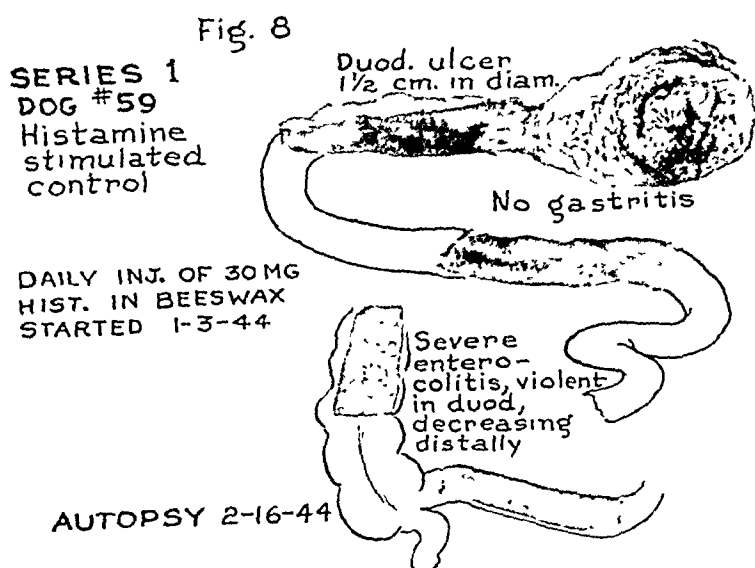
Mongrel male, weight 35 pounds (Fig. 7)

1/ 3/44 Daily injections of 30 mg. histamine in beeswax intramuscularly started

2/16/44 Sacrificed, autopsy performed

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	11.0	10.01	61.06	1.81
	½	35.5	140.90	158.26	1.40
	1	15.0	28.59	67.39	1.76
	1½	5.5	5.92	24.50	3.35
	2	0.5	0	20.42	Sample too small
12/15/43	Fasting	37.0	38.19	46.56	1.66
	½	66.0	102.10	118.44	1.24
	1	50.5	85.56	95.57	1.24
	1½	1.7	19.06	26.55	2.30
	2	2.8	2.04	7.35	1.44
12/17/43	Fasting	4.0	17.8	28.07	2.4
	½	45.0	110.3	124.6	1.54
	1	15.1	106.2	116.4	1.79
	1½	19.0	26.5	40.8	Not done
	2	6.0	30.6	46.96	1.7
12/21/43	Fasting	3.9	0	28.28	7.87
	½	66.0	113.94	124.97	1.71
	1	23.0	89.64	108.23	1.50
	1½	0.5	8.17	30.63	Too small
	2	1.2	2.04	10.21	Too small



EXPERIMENT 9

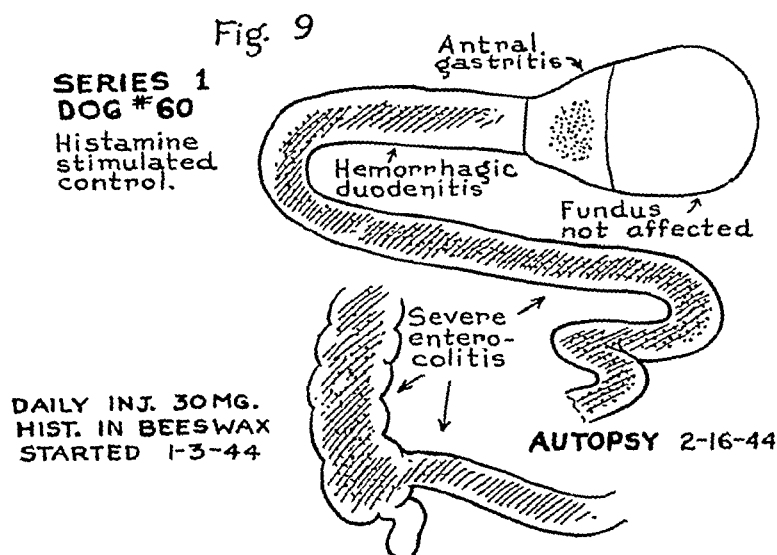
Series 1, Dog 59, Control Dog.

Mongrel male, weight 46 pounds (Fig. 8)

1/ 3/44 Daily injections 30 mg. histamine in beeswax started
2/16/44 Sacrificed, autopsy

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	5.5	42.27	63.10	1.60
	½	47.0	140.90	156.21	1.38
	1	52.0	134.77	146.00	1.39
	1½	5.3	1.84	5.92	5.96
	2	No specimen			
12/15/43	Fasting	0.8	0	12.25	7.10
	½	44.0	79.43	101.69	1.40
	1	8.0	7.96	40.64	1.61
	1½	16.0	9.60	17.97	5.13
	2	0.8	0	4.08	7.00
12/17/43	Fasting	4.5	0	20.4	7.11
	½	54.5	57.2	85.8	1.74
	1	44.5	81.7	100.06	1.54
	1½	3.0	6.9	18.7	3.05
	2	3.0	0	10.21	5.99
12/21/43	Fasting	16.0	0	40.43	7.17
	½	72.0	98.02	114.56	1.38
	1	25.5	83.93	97.81	1.65
	1½	13.0	26.55	41.04	1.85
	2	2.5	0	20.42	7.01



EXPERIMENT 10

*Series 1, Dog 60, Normal Control.**Mongrel male, weight 40 pounds (Fig. 9)*

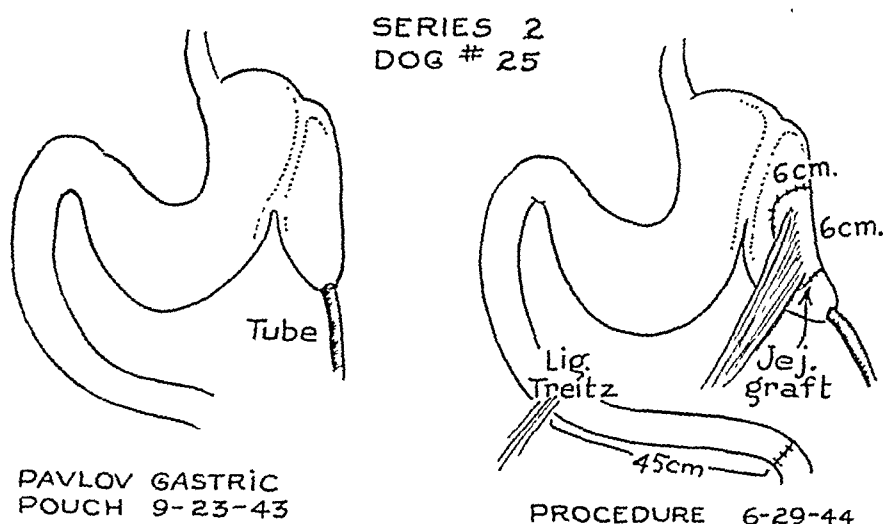
1/ 3/44 Daily injections of 30 mg. histamine in beeswax started
2/16/44 Sacrificed, autopsy

Results of Gastric Analyses

DATE	SAMPLE (HR.)	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
12/14/43	Fasting	1.8	6.0	18.02	3.68
	½	110.0	138.86	144.98	1.31
	1	49.0	85.97	93.93	1.43
	1½	2.3	25.01	29.61	1.74
	2	14.0	3.06	12.86	6.46
12/15/43	Fasting	2.5	0	10.21	7.51
	½	96.0	130.48	138.65	1.25
	1	18.0	30.64	51.05	1.69
	1½	3.8	1.45	2.92	4.31
	2	2.4	0	5.11	6.94
12/17/43	Fasting	6.5	2.04	12.48	4.41
	½	55.0	115.78	127.22	1.41
	1	44.0	99.85	111.90	1.41
	1½	12.0	9.80	15.31	2.8
	2	5.3	1.84	8.58	7.56
12/21/43	Fasting	4.5	0	20.42	7.64
	½	36.0	139.06	152.95	1.26
	1	142.0	132.53	159.48	1.46
	1½	4.8	17.02	37.86	1.97
	2	2.0	20.42	36.25	3.06

Series 2.—The second series consisted of two dogs, one of which had a Pavlov type of gastric pouch (Dog 25) and the other a Heidenhain pouch (Dog 156). The response of these two pouches to gastric secretagogues was studied and recorded. Following these control observations, a pedicled jejunal graft was applied to the pouch of each animal. After a suitable healing period, the animals were exposed again to the same secretagogues and the response was observed. Analyses of the contents of the gastric pouches were made after the dogs were subjected to a twenty-four-hour fast. Two one-hour samples were obtained from each dog, the secretagogues were then administered, and the total output of gastric juice was collected at hourly intervals for from three to twenty-four hours.

Fig. 10



EXPERIMENT 1

Series 2, Dog 25. Mongrel male, weight 49 pounds (Fig. 10)

8/24/43 Distemper vaccination
 9/23/43 Pavlov gastric pouch operation
 6/29/44 Jejunal graft applied to Pavlov pouch

Results of Gastric Pouch Analyses

DATE	SAMPLE	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
1/3/44	1	0.25	12.67	85.76	Too small
Stimulus: 0.5 mg.	2	0.30	34.00	51.05	Too small
histamine sub-	1 N	26.00	134.36	151.11	0.99
cutaneously	2 N	3.70	142.33	153.46	0.94
	3 N	1.60	84.41	110.27	1.20
1/5/44	1	0.15	6.81	61.26	Too small
Stimulus: 0.5 mg.	2	0.23	0	44.39	Too small
histamine sub-	1 N	5.0	134.16	147.02	1.07
cutaneously	2 N	2.0	130.68	141.92	1.08
	3 N	0.8	108.53	134.06	Too small
1/7/44	1	0.22	23.18	46.46	Too small
Stimulus: 0.5 mg.	2	1.5	0	40.80	3.43
histamine sub-	1 N	18.0	130.69	146.00	0.82
cutaneously	2 N	0.5	102.10	132.73	Too small
	3 N	0.12	84.74	170.51	Too small
5/29/44	1	2.4	0	122.47	3.63
Stimulus: 200 Gm.	2	1.1	0		Too small
horse meat fed	1 N	3.3	0	127.33	3.66
	2 N	6.0	55.6	129.66	1.50
	3 N	6.2	91.17	145.8	1.47
5/31/44	1	0.7	51.32	83.8	Too small
Stimulus: 200 Gm.	2	0.9	62.6	96.03	Too small
horse meat fed	1 N	6.0	107.11	122.08	1.61
	2 N	8.1	114.50	135.80	1.45
	3 N	7.4	119.94	139.97	1.37
6/2/44	1	No sample			
Stimulus: 200 Gm.	2	No sample			
horse meat fed	1 N	3.4	69.30	116.64	1.30
	2 N	3.2	85.51	121.22	1.17
	3 N	3.6	90.49	127.14	1.36
7/24/44	1	1.8	23.31	83.09	3.69
Stimulus: 0.5 mg.	2	1.6	28.24	79.96	2.76
histamine sub-	1 N	20.1	88.66	124.82	1.14
cutaneously	2 N	2.6	50.49	72.82	1.23
	3 N	0.98	7.98	17.56	1.0 (Hydrion)

EXPERIMENT 1.—CONT'D

DATE	SAMPLE	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
7/28/44	1	2.4	0	112.76	3.59
Stimulus: 0.5 mg. histamine sub- cutaneously	2	0.56	37.5	86.46	2.5 (Hydriion)
	1 N	24.0	126.75	152.79	1.27
	2 N	1.4	84.54	123.74	1.6
	3 N	0.24	53.80	89.66	3.0 (Hydriion)
8/4/44	1	2.0	0	48.42	4.02
Stimulus: 200 Gm. horse meat fed	2	1.5	0	35.86	4.38
	1 N	5	0	58.1	3.05
	2 N	4.5	38.25	81.29	1.76
	3 N	6.5	38.74	90.38	1.66
8/9/44	1	1.8	0	37.66	3.54
Stimulus: 200 Gm. horse meat fed	2	1.0	0	53.80	5.5 (Hydriion)
	1 N	5.6	29.05	81.77	2.10
	2 N	11.0	94.69	118.36	1.87
	3 N	12.5	100.07	121.59	1.64

EXPERIMENT 2

Series 2, Dog 156. Mongrel female, weight 55 pounds (Fig. 11)

4/ 6/44 Heidenhain pouch operation
6/29/44 Jejunal graft applied to Heidenhain pouch

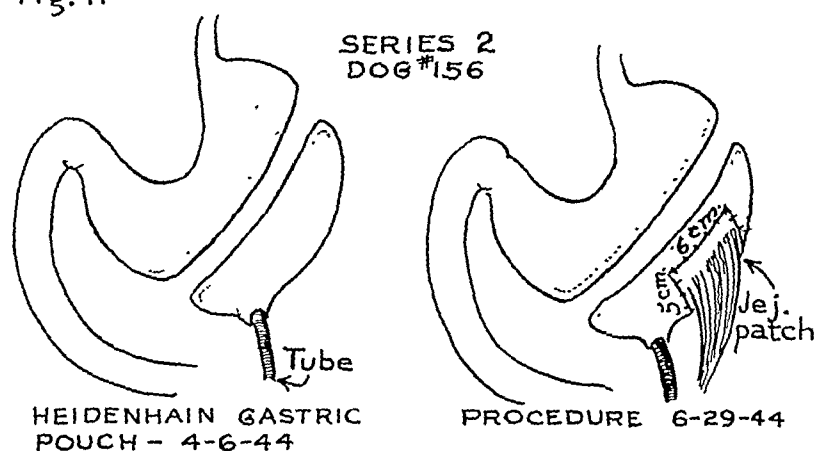
Results of Gastric Pouch Analyses

DATE	SAMPLE	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
5/8/44	1	0.6	0	32.37	6.0 (Hydriion)
Stimulus: 0.5 mg. histamine sub- cutaneously	2	1.2	0	21.38	5.87
	1 N	29.4	124.22	137.83	1.62
	2 N	14.3	111.78	127.33	1.34
	3 N	0.8	75.8	126.74	1.5 (Hydriion)
5/10/44	1	1.4	0	23.91	7.62
Stimulus: 0.5 mg. histamine sub- cutaneously	2	1.3	0	34.02	7.23
	1 N	25.5	99.14	126.36	1.36
	2 N	24.0	116.33	149.30	1.55
	3 N	1.9	16.23	27.02	2.09
5/12/44	1	0.1	19.44	97.2	Too small
0.5 mg. histamine subcutaneously	2	0.5	17.50	77.76	Too small
	1 N	27.0	118.58	130.44	1.11
	2 N	12.5	137.83	147.74	1.47
	3 N	0.4	21.38	106.92	Too small
5/15/44	1	3.0	0	15.16	6.83
Stimulus: 200 Gm. horse meat fed	2	1.4	0	28.19	7.47
	1 N	1.4	0	19.44	7.46
	2 N	2.0	92.91	97.20	1.36
	3 N	4.6	88.35	106.53	1.20
5/19/44	1	9.3	34.60	54.43	1.83
200 Gm. horse meat fed	2	0.38	55.51	86.09	Too small
	1 N	2.9	12.31	34.99	3.12
	2 N	9.0	58.32	74.26	1.61
	3 N	6.7	93.31	101.48	1.64
5/31/44	1	0.5	66.10	83.59	Too small
200 Gm. horse meat fed	2	3.4	3.21	29.74	2.55
	3	1.8	0	14.19	4.35
	1 N	1.1	0	10.69	Too small
	2 N	5.2	25.66	41.02	1.76
	3 N	0.4	112.75	129.28	Too small
	4 N	6.0	101.28	107.89	1.53
	5 N	0.45	119.56	139.00	Too small
	6 N	1.8	97.20	116.64	1.63
	7 N	5.1	123.44	134.33	1.48
	8 N	3.5	123.44	130.26	1.50
	9 N	3.3	119.56	130.25	1.50
	10 N	0.25	68.04	106.92	Too small

EXPERIMENT 2—CONT'D

DATE	SAMPLE	VOLUME (C.C.)	FREE ACID (DEGREES)	TOTAL ACID (DEGREES)	pH
7/21/44 Stimulus: 0.5 mg. histamine sub- cutaneously	1	8.0	0	101.58	3.95
	2	4.0	0	127.72	4.0
	1 N	59.4	111.01	142.75	1.12
	2 N	5.4	68.86	123.74	1.5
	3 N	1.4	22.28	102.76	2.52
7/28/44 Stimulus: 0.5 mg. histamine sub- cutaneously	1	1.8	0	34.67	4.84
	2	5.6	0	31.85	5.42
	1 N	19.0	113.63	141.82	1.54
	2 N	13.0	89.31	138.16	1.55
	3 N	2.1	51.43	111.9	1.5
	4 N	1.01	0	42.61	5.5 (Hydrion)
8/4/44 Stimulus: 200 Gm. horse meat fed	1	6.0	0	45.19	3.98
	2	4.5	0	26.29	6.58
	1 N	17.5	0	77.42	3.23
	2 N	12.5	32.28	96.81	1.89
	3 N	15.0	25.83	105.45	1.78
8/9/44 Stimulus: 200 Gm. horse meat fed	1	4.0	0	21.52	7.61
	2	4.2	0	23.21	7.41
	1 N	14.5	0	79.62	3.18
	2 N	15.9	86.0	119.44	1.90
	3 N	19.0	62.41	109.75	1.89
10/6/44 Stimulus: 0.5 mg. histamine sub- cutaneously	1	11.0	0	53.8	3.76
	1 N	61.0	29.0	93.0	2.4
	2 N	111.0	25.5	89.0	2.3
	3 N	12.0	0	19.0	4.8
10/10/44 Stimulus: 100 c.c. alcohol by stomach tube	1	0.31	0		3.28
	1 N	16.3	73.0	105.7	1.55
	2 N	3.05	49.7	87.0	1.19
	3 N	0.75	0	9.5	1.22
10/13/44 Stimulus: 200 Gm. horse meat fed	1	5.8	0	31.2	5.2
	1 N	10.25	0	43.0	4.32
	2 N	20.2	36.0	95.0	1.31
	3 N	22.0	52.0	93.0	1.17

Fig. 11



Series 3, Experiment 1.—The final experiment consisted of testing the irritating effect on duodenal mucosa of gastric juice obtained by histamine stimulation both from an ordinary type of Heidenhain gastric pouch and from another similar pouch which had been modified by the application of a jejunal graft. Gastric juice was collected from both of these dogs and saved for the experiment to be described. On 6/21/44, a male mongrel (Dog 184) was anesthetized with sodium pentobarbital,

and a three and one-half inch section of duodenum was isolated and exteriorized with its blood supply intact. The segment was opened along the antimesenteric border, and the mucosa was exposed by suturing the cut edges to the underlying abdominal skin. Immediately after the operation, the two collections of gastric juice were dripped, one from the Heidenhain pouch, the other from the Heidenhain pouch to which the jejunal graft had been applied, through similar nozzles, onto separate areas of the exposed duodenal mucosa (see Fig. 12).

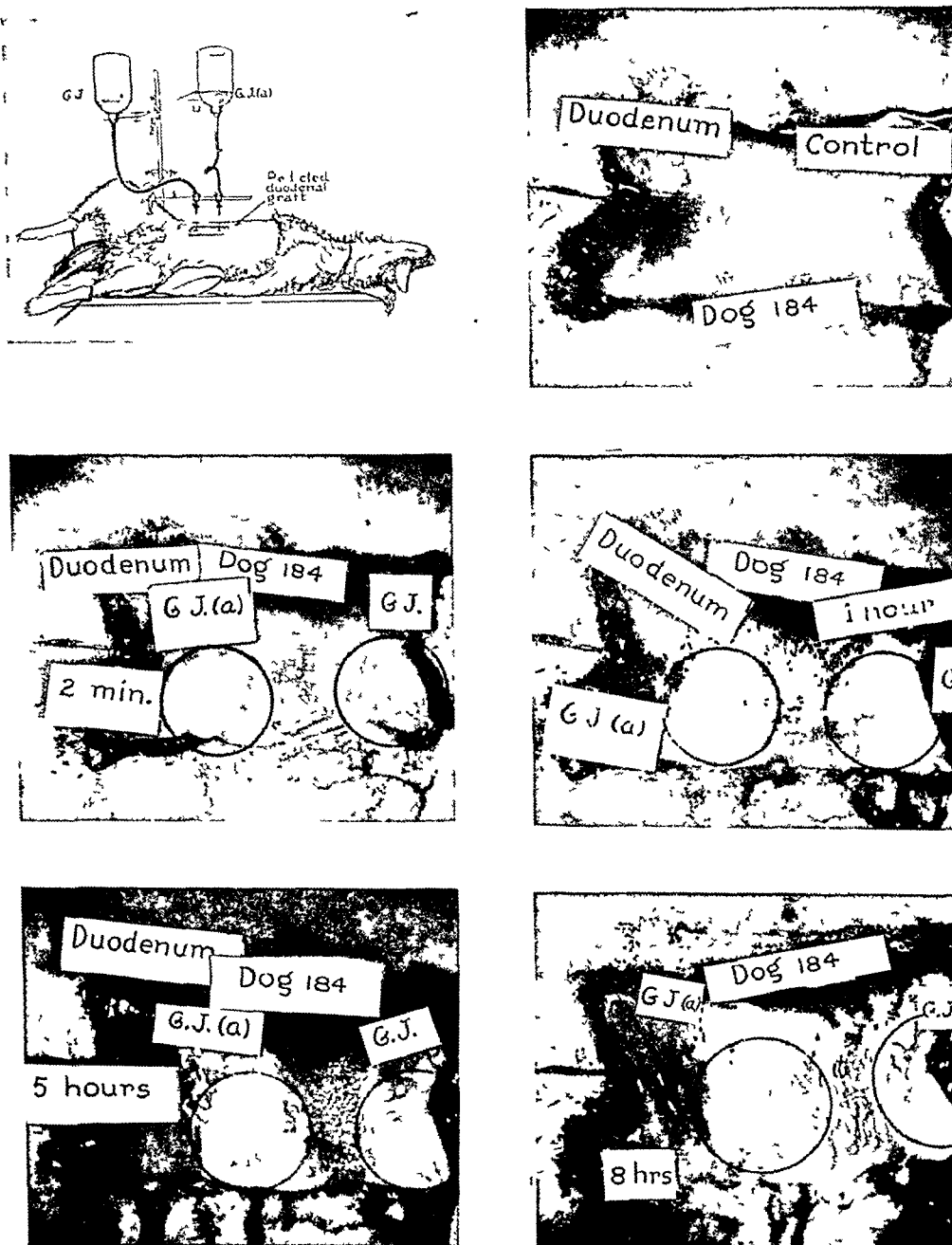


Fig. 12—The photographs show the progressive effect of two samples of gastric juice on duodenal mucosa. G.J. indicates the area exposed to secretion obtained from an ordinary Heidenhain type of gastric pouch (Dog 156 before application of jejunal graft). G.J. (a) indicates the area exposed to gastric juice obtained from a Heidenhain pouch into which a jejunal graft had been implanted.

The effects of the two samples of gastric juice on duodenal mucosa varied little. In both of the dripped areas, edema and blanching occurred within two minutes. During the first ten to fifteen minutes, the reaction to normal gastric juice seemed greater, but within one hour, necrosis, edema, and hematin staining were of equal intensity in both areas. After five hours, two thick, gray, hematin-stained, mucosal sloughs were present. Gentle removal of the necrotic tissue by scraping with the edge of a piece of cardboard revealed equal pin-point hemorrhages beneath both the sloughs. At the end of eight hours' exposure to the gastric juice obtained both from an ordinary Heidenhain gastric pouch and from a Heidenhain gastric pouch into which a pedicled jejunal graft had been implanted, the duodenal mucosa exhibited damage of equal extent in both areas.

COMMENT

Investigation of the effect of the pedicled jejunal graft on secretory activity indicates that an irregular, inconstant, therapeutically ineffective depression of gastric acid secretion occurs.

Adequate gastric analyses over a period of two hours after the administration of 0.5 mg. of histamine base show a somewhat subdued, but in the main quite ordinary, response-varying irregularly from dog to dog. A reversal of the histamine effect noted by Andrus and his associates was not observed on any occasion. In the continuous gastric hypersecretion experiments employing daily intramuscular injections of 30 mg. of histamine base in beeswax, the jejunal graft proved to be a locus of reduced resistance, and ulceration of the graft mucosa occurred in every dog with such a jejunal graft. In these same hypersecretion experiments, complete protection of the duodenal mucosa as observed by Andrus and his associates was not achieved in all cases. Duodenitis was observed in three out of five dogs with jejunal grafts applied to the stomach, given histamine in beeswax intramuscularly. In other words, it would appear that the jejunal graft itself when applied to the stomach is more sensitive to the acid peptic digestive juice than is the remainder of the stomach or the duodenum. Autopsies showed the pedicled blood supply of the graft to be satisfactory and intact in all animals. In experiments with the Heidenhain and Pavlov gastric pouches the implanted jejunal graft was found to be ineffective in regularly inhibiting gastric secretion from the isolated pouches. It may be fair to say that a small but inconstant depression of the acidity of the gastric secretion appears to attend attachment of the jejunal patch of the gastric pouch. Finally, gastric juice obtained from a Heidenhain pouch, modified by the application of a jejunal graft, proved to be as irritating as normal gastric juice when dripped onto exteriorized duodenal mucosa.

CONCLUSION

In conclusion, these experiments suggest that the jejunal graft is inefficient in controlling gastric and peptic secretion, and that it does not curb the digestive properties of gastric juice. In consequence, the pedicled jejunal graft is unlikely to be an effective therapeutic surgical agent in the treatment of ulcer. These experiments fail to lend any sup-

port to the thesis that this operation may supplant adequate gastric resection in the management of ulcer.

REFERENCES

1. Stefko, P., Andrus, W., and Lord, J. W., Jr.: The Effects of Jejunal Transplants on Gastric Acidity, *Science* 96: 208, 1942.
2. Andrus, W., Lord, J. W., Jr., and Stefko, P.: Comparative Effects of Gastroenterostomy and Pedicle Jejunal Graft on the pH of the Gastric Mucosa, *Proc. Soc. Exper. Biol. & Med.* 52: 99, 1943.
3. Lord, J. W., Jr., Andrus, W., and Stefko, P.: Comparative Effects of Pedicle Grafts From Different Levels of Intestinal Tract on pH of Gastric Mucosa, *Proc. Soc. Exper. Biol. & Med.* 52: 100, 1943.
4. Lord, J. W., Jr., Andrus, W., and Stefko, P.: Effects of Jejunal Transplants on Experimental Production of Peptic Ulcers, *Arch. Surg.* 46: 459, 1943.
5. Andrus, W., Lord, J. W., Jr., and Stefko, P.: Effects of Pedicle Grafts of Jejunum in the Wall of the Stomach on Gastric Secretion, *Ann. Surg.* 118: 499, 1943.
6. Andrus, W., Lord, J. W., Jr., Stefko, P., and Dingwall, J. A.: The Effect of Saline Washings of Isolated Jejunal Loops on Gastric Secretion, *Am. J. Physiol.* 140: 287, 1943.
7. Andrus, W., Lord, J. W., Jr., and Stefko, P.: A Possible Mode of Action of Pedicle Jejunal Grafts on Gastric Secretion as Indicated by Changes in pH of the Surface of the Mucosa of the Stomach, *Am. J. Physiol.* 141: 75, 1944.

AN ATTEMPT TO CONFIRM THE ALLEGED INHIBITORY EFFECT ON GASTRIC SECRETION OF JEJUNAL PEDICLE GRAFTS IN THE WALL OF THE STOMACH

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IT HAS been clearly established by several groups of workers¹⁻⁶ that a piece of jejunum implanted into the wall of the stomach is able to withstand the corrosive action of gastric juice if the vascular pedicle remains intact. These investigators did not, however, report upon the effect of the implants on gastric secretion.

In a series of recent papers,⁷⁻¹³ Andrus, Lord, and Stefko have reported that the implantation of a pedicle graft of jejunum into the wall of the stomach produces profound effects on gastric secretion. According to their observations, a jejunal pedicle graft implanted in the gastric wall tends to lower the fasting acidity and to reverse the response to histamine injection, that is, administration of histamine to a dog with a jejunal implant in the gastric wall is claimed to depress rather than increase gastric acidity. The stimulatory effect of alcohol on gastric secretion is also reported to be abolished or greatly reduced by these jejunal implants. Ileal and colic transplants into the stomach wall are stated to be ineffective, whereas jejunal transplants are somewhat more effective than duodenal transplants.

The mechanism of inhibition of gastric secretion by jejunal implants has been postulated to be due to a substance formed by the jejunal

associates. In each case animals were used in which the original operation for preparation of the gastric pouch had been performed a number of months or years previous to the implantation of the jejunal graft and on which a large number of control values for response to histamine were available. Following implantation of the jejunal pedicle graft into the pouch wall, histamine tests were performed at intervals of from 10 to 200 days postoperatively. The results of these experiments are set forth in Table III.

TABLE III

PRE- AND POSTOPERATIVE ACID SECRETORY RESPONSE DURING ONE HOUR AFTER HISTAMINE STIMULATION IN GASTRIC POUCH DOGS IN WHICH A JEJUNAL PEDICLE GRAFT WAS IMPLANTED

DOG NUMBER	TYPE POUCH	PREOPERATIVE CONTROL				POSTOPERATIVE TESTS			
		NO. TESTS	V	F	T	NO. TESTS	V	F	T
1	Entire stomach	11	22.4	79.0	86.2	12	32.6	118.0	129.0
2	Entire stomach	14	30.4	95.4	103.9	5	29.0	86.5	94.3
3	Pavlov	4	51.4	200.9	214.2	4	48.0	184.4	196.8
4	Heidenhain	12	22.0	84.2	93.8	6	25.0	96.5	106.1

V, Volume in cubic centimeters.

F, Free acid in milligrams of HCl.

T, Total acid in milligrams of HCl.

The integrity of the jejunal graft was determined in three cases by sacrificing the animals and examining the excised specimens. On the fourth animal the vitality of the graft was verified by exploratory laparotomy.

Comment.—In none of the four animals provided with a jejunal implant in the gastric pouch was a significant decrease in histamine-stimulated gastric secretion noted.

Part III. Implantation of Jejunal Pedicle Grafts Into the Intact Stomach of the Dog.—

Inasmuch as we were unable to find any evidence of inhibition of secretion by jejunal implants or jejunal washings in gastric pouch dogs we proceeded to study the effect of jejunal pedicle grafts in the intact stomach. Six normal mongrel dogs were trained to lie on a soft pad with a small (Rehfuss) stomach tube in place. Starvation for twenty-four hours preceded each test. The gastric residue was removed and the basal secretion collected over a ten-minute period by continuous gentle suction from a glass syringe. One milligram of histamine dihydrochloride was then injected subcutaneously and the gastric secretion collected by continuous suction for one hour, the samples being divided into six ten-minute periods. Three control tests were performed on each dog and then a pedicle graft of upper jejunum was implanted into the gastric wall in the manner described by Andrus and his associates.¹¹ This consisted in the resection under morphine-ether anesthesia of an area of the anterior wall of the stomach approximately 4 by 6 cm. in size, about midway between the pylorus and cardia, and the implantation into this defect of a pedicle graft of upper jejunum with its circulation intact. This was obtained by isolating a segment approximately 6 cm. in length, which was then opened along its antimesenteric border and sutured into the gastric window with silk. The continuity of the jejunum was restored by end-to-end anastomosis.

TABLE IV

ACID SECRETORY RESPONSE TO HISTAMINE DIHYDROCHLORIDE (1 Mg.) BEFORE AND AFTER IMPLANTATION OF JEJUNAL PEDICLE GRAFT INTO STOMACH

(Average of Three Tests Pre- and Three to Five Tests Postoperatively)

	10 MIN. BEFORE HISTAMINE		0-20 MIN. AFTER HISTAMINE			0-60 MIN AFTER HISTAMINE		
	AV. VOL. (C.C.)	AV. FREE ACID (C.U.)*	AV. VOL. (C.C.)	AV. FREE ACID (C.U.)	AV. FREE ACID OUTPUT (mm)†	AV. VOL. (C.C.)	AV. FREE ACID (C.U.)	AV. FREE ACID OUTPUT (mm)
Dog 1								
Preoperative	8	8	23	85	2.0	112	114	12.8
Postoperative	12	50	34	82	2.8	120	120	14.4
Dog 2								
Preoperative	3	0	30	106	3.2	115	137	15.8
Postoperative	13	19	49	79	1.2	140	97	13.6
Dog 3†								
Preoperative	7	34	38	110	4.2	127	126	16.0
Postoperative	3	5	19	64	3.9	78	88	6.9
Dog 4								
Preoperative	12	4	25	90	2.3	107	114	12.2
Postoperative	3	12	29	65	1.9	124	101	12.5
Dog 5								
Preoperative	8	0	26	68	1.8	92	87	8.0
Postoperative	4	20	34	59	2.0	116	82	9.5
Dog 6								
Preoperative	4	61	15	95	1.4	87	105	9.1
Postoperative	4	53	33	117	3.9	119	116	13.8
Av.								
Preoperative	7.0	18	26	92	2.5	107	114	10.6
Postoperative	7.1	27	33	77	2.6	116	101	11.6

*C. U., clinical units.

†mm, millimols.

†When this animal was anesthetized and autopsied a partial obstruction was found at the site of the end-to-end anastomosis in the intestine with dilation and hypertrophy above.

Dogs 2 and 3 showed considerable enterogastric regurgitation in some of the tests.

Ten days to 2.5 months after operation three to five histamine gastric analyses were performed on each animal by the same technique as that used in the preoperative controls.

After all analyses were completed, the animals were sacrificed and the stomach immediately fixed in formalin. Histologic sections were prepared to ascertain the condition of the jejunal graft. In every case normal jejunal mucosa was found. The position of the jejunal patch on the anterior gastric wall is demonstrated in the roentgenogram (Fig. 1) showing outpouching of the wall by the barium meal at this point. The size of the jejunal implant is shown in the picture of the gross post-mortem specimen of one of the stomachs (Fig. 2).

The averaged results of the preoperative and postoperative tests on each dog are presented in Table IV.

Comment.—The implantation of a jejunal pedicle graft into the intact stomach of the dog produced no consistent and significant decrease in acid secretion in response to histamine.

DISCUSSION

We have repeated the experiments of Andrus, Lord, and Stefko on the effect of jejunal implants in the gastric wall on acid secretion in response to histamine. Our results give no indication of an inhibitory effect.



Fig. 1.—Roentgenogram of barium sulfate in the stomach of a dog with a jejunal pedicle graft. The edges of the graft are indicated by the arrows.



Fig. 2.—Photograph of necropsy specimen of stomach with jejunal implant in the fundic area. The scale reads in centimeters.

Perfusion of vagally innervated and vagally denervated gastric pouches with freshly prepared saline washings of the duodenum and jejunum did not affect the acid secretory response to histamine.

Similarly, no decrease in acid secretion in response to histamine was noted in four dogs with gastric pouches into which a piece of upper jejunum was implanted.

In four out of six animals in whom jejunal pedicle grafts were implanted in the wall of the in situ stomach, no significant depression of the secretion of HCl in response to histamine was noted. In the other two animals of this series (Dogs 2 and 3, Table IV) a moderate decrease in the acid *concentration* was noted postoperatively. However, the explanation for the decrease in acid concentration of drainage recovered from the stomach in these two animals was apparent and can be accounted for by the nausea and retching, with regurgitation of bile-stained duodenal contents into the stomach, which not infrequently occurred during the postoperative tests on these animals. However, even in those tests in which enterogastric regurgitation reduced the acidity of some of the samples of gastric contents, the acid values returned to the usual high levels when retching subsided. Furthermore, these two animals in which retching occurred during most of the postoperative tests gave responses as high as the preoperative control values in those postoperative tests in which retching did not take place.

The cause for the increased tendency for retching and enterogastric regurgitation after histamine injection in certain dogs after the operation of jejunal pedicle graft is not obvious.

In only one animal (Dog 3, Table IV) did a decrease in both volume and acid concentration occur postoperatively. It is of interest to note that when the animal was sacrificed a partial obstruction of the bowel due to overgrowth of scar tissue at the site of end-to-end jejunal anastomosis was found in this dog. From prior experience in the performance of many end-to-end anastomoses in the dog, we have found that this occurs in approximately one out of thirty dogs. The possible significance of this finding in relation to the depression of gastric secretion in this animal is conjectural, although it is known that vomiting inhibits the secretory response to a meal and histamine.

It is particularly noteworthy that although the average volume and average concentration show moderate variation between preoperative and postoperative values, the total output of acid (volume times concentration) is not markedly altered.

Andrus and his associates studied gastric secretion for only twenty minutes after histamine injection. Inasmuch as only about one-fourth of the total secretory response to 1 mg. of histamine occurs in the first twenty minutes we have carried out our tests to one hour. It is to be emphasized, however, that even in the twenty-minute period following histamine injection we noted no significant depression of gastric secretion after the operation of jejunal implantation.

The question arises: If, as postulated from the observations of Andrus, Lord, and Stefko, the jejunum did secrete into its lumen a substance which on bathing the gastric mucosa inhibited gastric secretion, what could be the function of such a substance in normal physiologic economy? One could comprehend the function of such a substance

if it were secreted into the duodenal juice which has ready access to the stomach through the mechanism of enterogastric regurgitation. However, according to their observations, jejunal implants are more active than duodenal.

We are unable to suggest a possible cause for the discrepancies between our results and those of Andrus and his associates.

SUMMARY

Implantation of a jejunal pedicle graft into the wall of the stomach or perfusion of the stomach with jejunal washings does not significantly alter the acid secretory response of the stomach to histamine stimulation in the dog.

The authors wish to express their gratitude to Mr. Sam Baker and Dr. Jean Rea Wooley for their assistance in certain phases of this work.

REFERENCES

1. Marie, P., and Villandre, C.: *J. de physiol. et de path. gén.* 15: 602, 1913.
2. Mann, F. C.: *J. Med. Research* 35: 289, 1917.
3. De Takats, G., and Mann, F. C.: *Ann. Surg.* 85: 698, 1927.
4. Morton, C. B.: *Ann. Surg.* 85: 879, 1927.
5. Morton, C. B.: *Ann. Surg.* 87: 401, 1928.
6. Dragstedt, L. R., and Vaughn, A. M.: *Arch. Surg.* 8: 791, 1924.
7. Stefko, P., Andrus, W., and Lord, J. W., Jr.: *Science* 96: 208, 1942.
8. Andrus, W., Lord, J. W., Jr., and Stefko, P.: *Proc. Soc. Exper. Biol. & Med.* 52: 99, 1943.
9. Lord, J. W., Jr., Andrus, W., and Stefko, P.: *Proc. Soc. Exper. Biol. & Med.* 52: 100, 1943.
10. Lord, J. W., Jr., Andrus, W., and Stefko, P.: *Arch. Surg.* 46: 459, 1943.
11. Andrus, W., Lord, J. W., Jr., and Stefko, P.: *Ann. Surg.* 118: 499, 1943.
12. Andrus, W., Lord, J. W., Jr., Stefko, P., and Dingwall, J. A.: *Am. J. Physiol.* 140: 287, 1943.
13. Andrus, W., Lord, J. W., Jr., and Stefko, P.: *Am. J. Physiol.* 141: 75, 1944.
14. Butler, D., Hands, A. P., and Ivy, A. C.: *Am. J. Physiol.* 139: 3, 1943.

THE INDICATIONS FOR OPERATION IN CASES OF PEPTIC ULCER FROM THE INTERNIST'S POINT OF VIEW

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THAT articles on various aspects of ulcer of the stomach and duodenum continue to appear in large numbers indicates, perhaps, that some of the problems are not capable of final solution. Certainly most of the questions about peptic ulcer are not to be answered by exact methods; they remain matters of opinion and hence there are often strong differences among doctors as to matters of procedure. In a symposium published seven years ago in this Journal, I expressed my views¹ on the indications for operation in uncomplicated peptic ulcer. On re-reading that article I see no reason to alter greatly what was said; indeed it would be tedious to review exactly the same material. However, it may be of interest to surgeons, who will make up the bulk of the readers of the present symposium, to have the point of view of a "nonoperating" doctor on some of the indications for surgical interference.

Obstruction.—Pyloric obstruction has been regarded by most physicians as an indication for surgical treatment whether by gastroenterostomy or pyloric resection. It is interesting, therefore, to find a recent article in a surgical journal in which this point of view is questioned.² However, few will believe that those instances of vast dilation of the stomach associated with masses of scar tissue which throttle the pylorus can be dealt with by means other than surgical. It is in the borderline cases that nice decisions have to be made. The point is best brought out by considering the reversible and irreversible elements which enter into the production of clinical pyloric stenosis. Scarring and anatomic narrowing can hardly be altered but inflammation of the mucous membrane with edema and spasm, so often associated with fibrous stenosis and acting as a last straw to render the obstruction complete, are usually amenable to treatment. Hence, one may see surprising remissions in patients who at first seemed in a desperate plight. It will rarely be necessary to do an emergency operation and the situation should be re-evaluated after a trial period of medical therapy. The following plan has worked well in our clinic: The stomach is emptied by washing with many liters of normal saline solution using a large (Ewald) tube. The procedure must be thorough if the final dregs of retained material are to be reduced to a minimum. The washing is repeated each evening for several days during which the patient is maintained by parenteral alimentation with glucose, saline solution, and, if necessary, some form of protein digest.³ After two to four days it is usually found that the volume of residual secretion has decreased to less than 100 c.c., and that fluids are passing through in the pylorus. Further proof of this may come from the regurgitation of bile through the duodenum into the gastric washings. One may now begin to feed small amounts of concentrated liquid nourishment during the day but the stomach should still be thoroughly washed each night several hours after the last feeding. This procedure controls stasis and allows the stomach to regain its tone while edema and spasm subside and the pyloric lumen widens. Next it is necessary to decide whether the results have been good enough to justify continued medical treatment or whether operation is necessary. General clinical improvement, roentgen examination of the stomach with umbrathor to show the irreducible degree of obstruction and stasis, the patient's desire or ability to cooperate in a long-time medical regimen, his economic means, his age, and the availability of the best surgical skill all enter into the making of a difficult decision. It is our feeling, however, that if any doubt exists at this point about the success of medical therapy, operation should be done.

Hemorrhage.—Debate as to when one should operate for hemorrhage from peptic ulcer will probably always go on because in the end it comes down to judgment in the individual case and no formula based on statistical experience is entirely satisfactory. Most internists, however, would subscribe to the following propositions: A single bleeding from peptic ulcer in a young person, even if the bleeding is large, rarely kills, and medical treatment is usually satisfactory. The availability of blood and red blood cell concentrates for transfusion is comforting to the doctor under these conditions. In elderly people, on the other hand, severe bleeding, especially if persistent, with the possibility of erosion of a calcified vessel in the base of the ulcer is much more likely

to demand surgical interference. At any rate, every case of this sort should be followed jointly by internist and surgeon, and operation should be done if the bleeding gains headway in spite of transfusion. The internist should remember the surgeon's troubles—a patient usually in poor condition, a stomach full of blood, the difficulty of locating the lesion, especially if in the duodenum, and finally the technical complexities of operation under these conditions.

Another indication for operation is, of course, the occurrence of repeated persistent bleeding over a long period of time even though there never is a threat of exsanguination.

The whole subject has been ably discussed by Heuer⁴ in his recent book which is based on a study of carefully collected cases and not on vague impressions. We are in agreement with Heuer that, regardless of theory, a period of fasting for the first few days after a big bleeding is usually safer than feeding.

Ulcer and Cancer.—In the past, one of the strongest reasons for excising a gastric ulcer has been fear lest it should become malignant. That such malignant transformation commonly occurs was generally believed and debate centered only on the exact frequency. Recently the pendulum has swung to the other extreme. The work of Mallory⁵ and others⁶ on "carcinoma in situ" which shows that cancers may exist in the stomach for long periods without much change before ultimate rapid growth takes place, and the clinical studies of Palmer,⁷ have thrown doubt on the frequency of "cancer ex ulcere." These observations tend to show that the usual situation is in fact ulceration in a cancer already present and not cancer developing in an old ulcer. It would seem unreasonable, however, as pointed out by Heuer, to adopt too extreme a position. It is well known that cancer may arise in old leg ulcers, in pulmonary cavities, in brief in many situations where chronic ulceration exists and one surely cannot say that cancer will never develop in a gastric ulcer.

But even if one assumes that cancer is not likely to arise it is often difficult to say whether an "ulcer" when first discovered is benign or is in fact an ulcerated cancer. Here the gastroscope and modern roentgenography are, of course, very helpful but we believe the rule still holds good that any ulcer of the stomach which does not show definite signs of healing after three weeks of careful treatment should be dealt with surgically because of the possibility of cancer in disguise. Even then, one may be misled by apparent improvement of a lesion which is fundamentally cancerous (Eusterman).⁸

Intractable Indigestion.—In a discussion in the previous symposium¹ we sustained the thesis that intractable symptoms even in the absence of bleeding, obstruction, or perforation were an indication for operation. We still believe that position to be sound in many cases. However, one should point out that there has been a shift in emphasis in the whole philosophy of peptic ulcer and indigestion in the past few years, especially as a result of war experiences,⁹ and this may alter one's attitude toward surgical indications. Peptic ulcer, in brief, has been definitely brought into the domain of psychosomatic medicine. The interesting observations of Draper,¹⁰ the important work of Wolf and Wolff¹¹ which amplifies with modern methods what Beaumont saw a hundred years ago, and the clinical studies of innumerable internists and psychiatrists¹²

have shown beyond question the important part which psychologic influences play not only in promoting symptoms, but also through the mechanism of spasm and hyperemia in actually causing the breakdown of tissue. The position seems so securely established that most patients probably deserve technical psychiatric consideration before being subjected to operation. In different cases, however, either the psychic or the somatic component may predominate. If the psychogenic factor is prominent one should be cautious about operation; if such factors seem inconsequential, operation to excise a scarred and irritable duodenal cap and break up indigestion reflexes by creating a wide stoma is, we believe, sound practice even if no bleeding or obstruction exists.

Two patients seen recently illustrate the point: Both had long-standing indigestion; spastic deformed duodenal caps were shown by x-rays; both had responded to hospital therapy but relapsed under their usual activities. Neither had bled or shown signs of obstruction. In one no psychogenic material could be brought out; he agreed in a matter-of-fact way to any sort of interference if it would give relief. The second patient yielded a mine of trouble on psychiatric study; his symptoms were done away with not by operation but by a stay in the psychiatric ward.

SUMMARY

Many of the problems of peptic ulcer are not capable of solution by exact methods; they remain matters of opinion upon which physicians will differ. The points brought out with reference to indications for operation may be summarized briefly as follows.

What at first appears to be total pyloric stenosis may in fact be partly due to reversible spasm and edema. Hence, operation should rarely be done until measures to relieve such spasm and edema have failed.

From the surgical standpoint the great problem of hemorrhage is to recognize that it has become "intractable" before it is too late to save life by operation. Since a first hemorrhage in a young person is rarely fatal one may put off operation longer than in an elderly person with persistent bleeding. Transfusion of concentrated red blood cells may be lifesaving in preparing a patient who has bled severely.

Cancer develops so rarely in gastric ulcer that prophylactic excision is not usually indicated. However, ulcers apparently benign which fail to heal promptly may in fact be cancer and should be removed by gastric resection.

With the recognition that peptic ulcer is often a psychosomatic problem, operation will be done less often than formerly for indigestion (without obstruction or hemorrhage), but operation still has a place in refractory cases with insignificant psychiatric symptoms.

REFERENCES

1. Bloomfield, A. L.: The Indications for Operation in Cases of Uncomplicated Peptic Ulcer, *SURGERY* 2: 710, 1937.
2. Hinton, J. W.: The Intractable Duodenal Ulcer: Evaluation of Surgical Procedures, *Ann. Surg.* 117: 498, 1943.
3. Altschuler, S. S., Sahyun, M., Schneider, H., and Satriano, D.: Clinical Use of Amino Acids for the Maintenance of Nitrogen Equilibrium, *J. A. M. A.* 121: 163, 1943.
4. Heuer George J., Holman, Cranston. and Cooper, William: The Treatment of Peptic Ulcer, Philadelphia, 1944, J. B. Lippincott Company.

5. Mallory, Tracy B.: Carcinoma in Situ of the Stomach and Its Bearing on the Histogenesis of Malignant Ulcers, *Arch. Path.* 30: 348, 1940.
6. Palmer, W. L.: Duration of Cancer of the Stomach, *Gastroenterology* 1: 723, 1943.
7. Palmer, W. L.: See discussion in Portis, Sidney A.: *Diseases of the Digestive System*, Philadelphia, 1941, Lea & Febiger, p. 511.
8. Eusterman, G. B.: Carcinomatous Ulcer, *J. A. M. A.* 118: 1, 1942.
9. Dunn, W. H.: Gastroduodenal Disorders: An Important Wartime Medical Problem, *War Med.* 2: 967, 1942.
10. Draper, G.: The Emotional Component of the Ulcer Susceptible Constitution, *Ann. Int. Med.* 16: 633, 1942.
Draper, G., and Touraine, G. A.: The Man-Environment Unit and Peptic Ulcer, *Arch. Int. Med.* 49: 616, 1932.
11. Wolf, S., and Wolff, H. G.: Evidence on Genesis of Peptic Ulcer in Man, *J. A. M. A.* 120: 670, 1942.
12. Nittlemann, B., and Wolff, H. G.: Emotions and Gastro-duodenal Function, *Psychosom. Med.* 4: 5, 1942.

THE MEDICAL TREATMENT OF PEPTIC ULCER REFRACTORY TO SIPPY THERAPY*

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THE entire etiology of peptic ulcer is as yet unknown. However, no matter what the ultimate cause may be, there is no doubt that the "acid-pepsin factor" is the immediate agent of the ulcerative process. There is considerable evidence to support this view. For example: (1) Peptic ulceration occurs only in areas exposed to active gastric juice, that is, the lower part of the esophagus, the stomach, the upper third of the duodenum, the jejunum (following gastroenterostomy), and Meckel's diverticulum (when it contains parietal cells). (2) Peptic ulcer does not occur in the presence of a complete achlorhydria (as proved with histamine and neutral red). (3) Recurrent ulceration is prevented by gastric resection when this operation results in an achlorhydria. Conversely, marginal jejunal ulcers may occur when the acid is not eliminated.

On the other hand, there exists a considerable number of predisposing and aggravating factors without some of which peptic ulcers cannot be formed even by a highly potent gastric juice. Among these must be included the following: (1) emotional upsets which cause certain localized circulatory disturbances, prolonged gastric retention, and excessive and prolonged gastric secretion (especially during the night); (2) diminished tissue resistance associated with inadequate nutrition, circulatory disturbances, toxic infectious processes, and inadequate mucous secretion; (3) motor effects in the stomach, such as spasm, hypermotility, and atony; (4) impaired neutralization of acid gastric chyme by decrease of mucus, mucoid secretion, or duodenal

Received for publication, Nov. 2, 1944.

*This work was carried on in part with the support of John Wyeth and Brother, Inc.

regurgitation of bile, pancreatic secretion, and intestinal secretion; (5) certain endocrine influences; (6) postoperative states, such as gastroenterostomy and partial gastrectomy with persistent free acidity; (7) miscellaneous factors, including excessive use of alcohol or tobacco, food irritants, extensive burns, constitutional factors.

It must be emphasized that, despite all the arguments in favor of the acid-pepsin theory of ulcer formation, no valid claim can be made that this factor stands out as "the specific cause" of peptic ulcer disease. Rather, active gastric juice must be considered as the agent by which the lesion itself is produced in a stomach normally impervious to its action, but which is made susceptible to such ulceration by suitable predisposing factors. Ample evidence for this is afforded by the fact that perhaps 75 per cent of all patients with gastric ulcer and 20 per cent of those with duodenal ulcer have low or normal acidities, whereas some individuals manifest typical hypersecretory curves *without* objective evidence of ulceration. The occurrence of peptic ulcer in patients with normal or low gastric acidity appears to present a contradiction, but it may be explained by considering ulceration as the result of *peptic* digestion rather than acid irritation.¹

In view of our inability to control adequately the predisposing factors, it has become the aim of most current therapeutic procedures, medical and surgical, to eliminate the immediate agent of tissue destruction, the "acid-pepsin factor." The most common examples of such procedures entail the following: (1) antispasmodics (for example, atropine) to lessen the retention of gastric secretion; (2) alkalis, to neutralize the hydrochloric acid; (3) high-fat diets, to inhibit acid secretion; (4) frequent feedings, to absorb and dilute the acid; (5) sedatives to inhibit the nervous secretion of acid and pepsin; (6) gastric aspiration, to remove excess retained gastric juice; (7) partial gastrectomy, to reduce the output of acid and pepsin; (8) gastroenterostomy, to increase the neutralization of acid by duodenal regurgitation; (9) surgical vagotomy, to lessen the output of both acid and pepsin in the psychic phase of secretion.

Chronic peptic ulcer is a lifelong disease and only a small percentage of patients are cured medically, while a fair percentage go through life with mild symptoms. The remainder, about 25 per cent, are refractory and require intensive medical or surgical therapy. For this purpose, the usual Sippy therapy seems inadequate, because it does not control the acidity between the meals. Studies from this hospital reveal that there is a very high secretion of acid during the night,^{3, 4} even while the patient is on Sippy treatment during the day. Frequent Sippy feedings may in themselves serve as an added stimulus to the nervous phase of acid secretion and may not allow sufficient functional rest, motor or secretory. Other disadvantages of Sippy therapy are as follows: (1) The diet is nutritionally deficient and is increased too slowly. (2) It necessitates an in-bed routine, either in the hospital or the home. (3) Remissions after Sippy treatment are short, and recurrences are often severe. (4) The large amount of absorbable alkalis used may lead to a harmful systemic alkalosis in the presence of renal dysfunction. (5) It does not constitute an adequate means of effecting interdigestive neutralization, especially of the night secretion.

Various other methods have been used to control the harmful nocturnal hypersecretion, usually before retiring, but they are also often ineffective. These include gastric aspiration, atropine, sedatives, olive oil, alkalis given separately or in combination. As a result of the failure of these measures to control the symptoms associated with the night secretion, there arose the idea of *continuous intragastric drip therapy throughout the twenty-four hours.*² As originally introduced, this treatment was defined as a "local intubation ulcer therapy based on the principle of a continuous, adequate, intragastric neutralization of the free hydrochloric acid between the meals and during the night by a milk-soda drip." With the advent of nonabsorbable alkalis in 1934, various preparations of aluminum hydroxide and phosphate gels were included in the drip treatment.⁵ These colloids, besides preventing alkalosis, are antipeptic and astringent, and can be substituted for the milk-sodium bicarbonate mixture wherever the latter is contraindicated, as in cases of an allergic reaction or an idiosyncrasy toward milk. However, the nutritive value of milk and the simplicity of the apparatus required for its administration favor its use whenever conditions permit. A mixture of milk and alumina gel has also been tried and found adequate.

Physiologic evidence regarding the value of intragastric drip therapy was established by a series of studies which showed the efficacy of the method in reducing gastric acidity.⁶ With both the milk-sodium bicarbonate and aluminum hydroxide or aluminum phosphate gels, an average nocturnal, interdigestive pH of 1.4 was elevated to a mean pH of 3.5 to 4.0, thus inducing a harmless achlorhydria between the meals and during the night. At this higher pH, about 90 per cent of peptic activity is also eliminated. Hence, the continuous drip procedure affords a method for the continuous neutralization throughout the twenty-four-hour cycle, thus achieving the *sine qua non* of ulcer healing, namely, a continuous achlorhydria.⁷

An experience of thirteen years with the continuous intragastric drip method has demonstrated the clinical efficacy of this most recent advance in the medical therapy of peptic ulcer. Certain practical points in the application of this therapeutic procedure may be noted:

1. The technique is learned quickly so that nearly all the patients can administer it to themselves at home during the night. Individuals in our outpatient group are often unable for economic reasons to discontinue their daily routine, and enter the hospital whenever they have a severe recurrence. Using a vessel similar to the ordinary enema can as a milk container, and a Murphy drip indicator, they can operate the drip at home during the night and carry on their work during the day, thus continuing a "home cure" for as long as may be necessary.

2. Most of these patients are "tube broken," having had various gastric analyses performed upon them, so that they do not find the method drastic or difficult. With the recent introduction of the latex tube⁸ instead of the semirigid Levin tube, patients are able to use the drip over long periods of time without distress. Whichever tube is employed, the patient is taught to pass the tube on himself so that he does not have to depend on a nurse or doctor. The details of the drip therapy technique have been fully described elsewhere.⁹

3. Moderate and severe cases require the drip between the meals as well as during the night, whereas mild cases require it only during the night.

4. Continuous twenty-four-hour drip therapy is rarely necessary; usually, it is reserved for patients with intractable pain, during the first twenty-four or forty-eight hours, and especially for those with nocturnal pain.

5. Three liberal bland "ulcer" meals are given, preceded by atropine and phenobarbital, and followed with aluminum gel. This regime, in combination with the interdigestive drip, permits adequate tissue nutrition and provides an optimal neutralization.

6. There is usually a rapid loss of symptoms, sometimes after only twenty-four hours.

7. Ulcer niches heal rapidly, and huge craters in the stomach have sometimes been found to disappear in less than three weeks, as proved by x-ray and gastroscopy. We have seen many very long remissions after this form of therapy, which is particularly significant in view of the refractory type of patient receiving this treatment.

8. It is the best method of controlling the distressing night symptoms of ulcer, without disturbing the patient's sleep.

9. It has helped avoid surgical therapy in a considerable number of cases. In fact, it is our opinion that no patient with uncomplicated ulcer should be operated upon until drip therapy has first been tried.

10. Large gastric ulcers, at first thought to be malignant, have sometimes been proved benign by the rapid diminution in size and the loss of symptoms, thus aiding in the differential diagnosis.

11. Should operation ultimately be decided upon after the intragastric drip therapy, the lesion will be found more easily resectable because of its smaller size and the decreased inflammation.

The ulcer patients who were refractory to the usual Sippy treatment and who subsequently responded to drip treatment, either with milk-soda or aluminum gel, in this hospital, now total about sixty. This group includes: elderly men with penetrating ulcers of long duration with short or no remissions; patients with uncontrollable night pains; individuals with recurring massive hemorrhage, usually treated surgically; patients who could not be treated surgically because of age and poor general condition, or who refused surgery; and those with unyielding, severe pains during the day. Ordinarily a group of refractory ulcer patients like these would be considered candidates for surgical therapy. As a result of the application of the continuous intragastric drip therapy, however, they lost their symptoms and showed objective evidence of healing of the lesion. That other clinics have had similarly good results with this mode of treatment is indicated by a recent statement of Eusterman's,¹⁰ that "the superiority of the drip method over conventional procedures is unquestionable, especially in the treatment of the more refractory lesions." Consequently, we are presenting detailed case reports on twenty-two of these sixty patients, chosen as representative of the entire group, in order to illustrate the successful application of this form of therapy to such refractory cases. It is hoped that this will stimulate the further study of therapeutic procedures along these lines.

ALUMINUM HYDROXIDE OR PHOSPHATE GEL DRIP CASES

CASE 1.—F. W. was a woman, aged 42 years. In 1929, x-rays revealed evidence of duodenal ulcer. Because of severe epigastric pain, anorexia, vomiting, and loss of twelve pounds, the patient was admitted in 1940 to The Mount Sinai Hospital. The present attack of four weeks' duration was unrelieved by the usually controlling dietary measures and Sippy regime. Free acid was 75mN (millinormal), total 90mN. The patient became entirely symptom-free on the aluminum phosphate drip for three weeks during the night and between meals. In addition to the duodenal deformity, gastrointestinal x-rays showed a small diverticulum of the second portion. A Rehfuess test was done after drip therapy; free acid was 40mN, total 56mN. The patient has done well for four and one-half years without any serious recurrence.

CASE 2.—F. D. R. was a man aged 38 years. The patient had a fifteen-year history of duodenal ulcer when admitted in 1940 for "intractable pain." There was a history of tarry stools in 1937, treated at another hospital. In the one and one-half weeks before admission, he had epigastric and back pain with loss of eight pounds and suffered night pain not relieved by Sippy therapy. Although surgery was strongly advised, he preferred medical treatment. He received the aluminum phosphate drip between meals and nightly for three weeks with relief of symptoms. Gastrointestinal series now showed duodenal irregularity with slight six-hour residue. He has been followed since in the out-patient department and continues well on diet and medication after four and one-half years.

CASE 3.—J. G. was a man, aged 36 years. The patient was admitted in 1940, with a ten-year history of heartburn, one hour after meals, relieved by soda. In the one and one-half years before admission he had epigastric pain, nausea, vomiting, back pain, anorexia, and loss of sixty-five pounds. For the last three weeks, pain was persistent with no response to milk or alkali, and night pain was a prominent feature. Gastrosocopy revealed a large, irregular gastric ulcer on the lesser curvature, extending from the anterior to the posterior surface with a nodular base, suspicious of malignancy. Free acid was 90, total 115mN. The patient received the continuous aluminum hydroxide drip at night and between meals for two and one-half weeks. Pain disappeared and the patient's condition was definitely improved coincident with the use of the drip. On repeating the gastrosocopy, the ulcer was one-third the original size, superficial and healing, and appeared definitely benign. Gastrointestinal x-rays failed to show the penetrating ulcer crater previously seen. The idea of surgery, considered at first, was dropped. The patient was followed in the outpatient department in 1942, and was well on ambulant regime.

CASE 4.—V. P. was a man, aged 49 years. The patient, with a two-year history of epigastric pain, complained of extremely severe and continuous pain in the two days before admission with radiation to the back and loss of thirteen pounds in the past five weeks. He failed to be relieved by Sippy treatment. He was admitted with marked direct and rebound epigastric tenderness. Gastrointestinal x-ray series revealed a gastric ulcer, five-eighth inches in size, on the posterior wall near the re-entrant angle on the lesser curvature. Gastrosocopy showed a deep ulcer, three-quarter inches in diameter, benign in appearance. Because the lesion was possibly malignant, aluminum phosphate drip was advised, although surgery was considered seriously. He received the drip between meals and at night for about three weeks, after which gastrosocopy showed ulcer only one-quarter inch in size, benign and healing. Surgery was not considered further, and he has been followed since in the outpatient department and is doing well, over two and one-half years after the drip therapy.

CASE 5.—W. R., a man, aged 32 years, entered the hospital in April, 1940, with a seven-year history of gnawing epigastric pain. X-rays showed a duodenal ulcer shortly after onset. Free acid was 94, total 110mN. Because of a three months' attack of severe pain unrelieved by Sippy therapy, he was placed on aluminum phosphate drip, between meals and nightly for three weeks, with rapid improvement and subsidence of pain and tenderness.

CASE 6.—S. D. was a woman, aged 43 years. The patient was admitted in October, 1940, with a six months' history of epigastric pain, worse in the past two months, when pain radiated to the back, usually at night. Sippy treatment failed to help the patient. She then received the aluminum phosphate drip for twelve days between meals and nightly. Free acid was 80, total 110mN, before drip treatment. This was reduced to a free acidity of 12mN, with no acid in six specimens after the drip. X-rays proved the presence of a duodenal ulcer. The patient improved definitely and was relieved of pain coincident with the use of drip therapy.

CASE 7.—R. R., a man, aged 53 years, was admitted November, 1940, with tarry stools, weakness, and dizziness for three days before admission. This was the patient's third hemorrhage in the past six years. He had been on Sippy therapy for several weeks before the hemorrhage. Evidence of bleeding with guaiac positive stools lasted one week. He received the aluminum phosphate drip day and night for over two weeks, with cessation in bleeding and steady improvement after the first week. The patient has remained well for two years. He was last seen in the middle of 1942.

CASE 8—G. M. was a man, aged 62 years. This patient had ulcer symptoms for twenty years. Ten years before admission he was operated on for an acute perforation of the ulcer. He remained well for a short period (two months) and then the symptoms recurred severely. For seven months he suffered from ulcer pains, particularly at night. He was treated in the hospital for four weeks with strict Sippy therapy. However, the night pains and pain and heartburn after meals persisted. X ray examination revealed two rather large ulcer niches in the duodenal bulb. There was a high gastric acidity (80mN). He was treated with aluminum phosphate gel drip with a rapid loss of symptoms. He continued the drip at night at home for eight weeks. X ray examination then revealed only a deformity of the bulb. The niches had disappeared. He has remained in perfect health since then, a period of two years.

MILK AND ALUMINUM GEL DRIP CASES

CASE 1.—M. R., a man, aged 27 years, with a five year history of duodenal ulcer, entered the hospital because of tarry stools. A second attack of melena occurred one year later. Free acid was 120, total 130. Operation was strongly urged, but refused. His third admission was in December, 1941, with a history of tarry stools and pain. Whereas formerly he had been treated with Sippy therapy, he was now given the aluminum hydroxide drip for nine days and milk drip for one week, day and night. Gastrointestinal series showed deformity of duodenal bulb with a small posterior wall crater. The patient has remained well for over three and one half years with no recurrence of pain or bleeding.

CASE 2—I. S. was a man, aged 57 years. The patient had a thirty five year history of peptic ulcer, with pain after meals and at night. Eight years before, tarry stools were passed, and subtotal gastrectomy was advised at that time, but refused. On the present admission, free acid was 98, total 110mN, and a radiograph showed a deformed bulb. Sippy therapy was discontinued and he was placed on the milk drip day and night for twelve days and the aluminum phosphate drip for six days. Marked relief, disappearance of pain, and increased appetite were obtained. Follow up: After four years, the patient continues to do well.

CASE 3—E. W. was a woman, aged 38 years. The patient had a two year history of epigastric pain and a particularly severe attack in the two months before admission, requiring a hypodermic of morphine for relief of back pain. X rays in the outpatient department one week before revealed a penetrating gastric ulcer. Gastroscopy showed a deep ulcer, 2.5 cm. on the posterior wall and lesser curvature of the stomach. When Sippy therapy failed to relieve her, she was started on the aluminum gel drip between meals and after one week received the milk drip during the day and night for two weeks. The patient was slow at the start to show improvement and surgery was considered. However, she continued with marked improvement, subsidence of pain, and gain of over ten pounds in weight. Follow up x rays showed a complete disappearance of the ulcer.

MILK DRIP CASES

CASE 1.—S. S. was a man, aged 42 years. After one year of typical ulcer symptoms, a severe gastric hemorrhage occurred. Three weeks later, an x-ray examination revealed a large penetrating ulcer at the angle. There was a high acidity (60mN). He was treated for six weeks with a strict in-bed Sippy therapy. Another series of radiographs showed that the ulcer was unchanged. Surgical therapy was then considered for a possible neoplasm. However, milk-soda drip was tried first. After four weeks of drip therapy, the niche had completely disappeared. He then continued the drip therapy at night for several more weeks. After that he was asymptomatic for one and one-half years. He then died suddenly from a heart attack. The autopsy revealed a scar of a healed lesser curvature ulcer.

CASE 2.—C. C., a man, aged 40 years, had severe ulcer symptoms for one and one-half years. He was then on Sippy therapy for two months. A moderately severe hemorrhage then occurred and the hemoglobin fell to 55 per cent. Radiographs revealed an ulcer niche in the duodenum. He was treated for three weeks with the milk-soda drip. He continued the drip only at night for one year. He has remained well with normal radiographs for nine years.

CASE 3.—I. H., was a man, aged 20 years. During the previous two years the patient had had four severe attacks of ulcer symptoms. On the fifth attack, a duodenal ulcer and a small gastric ulcer at the angle were demonstrable in the radiographs. Despite the strictest Sippy therapy, the symptoms grew worse and surgical therapy was advised. However, it was decided to try milk-soda drip therapy first. He was given the drip following meals and during the night. He lost the symptoms in forty-eight hours. After leaving the hospital, he continued the drip therapy in the College Infirmary at night through the college year. Three months after the institution of the drip therapy, radiographs revealed a normal stomach and duodenal bulb. This patient has remained in perfect health for three and one-half years.

CASE 4.—A. F., a man, aged 47 years, had typical ulcer symptoms for ten years, including a massive hemorrhage. For three months, he suffered with severe ulcer symptoms unrelieved by Sippy therapy and foreign protein injections. Radiographs then revealed an ulcer niche in the stomach at the angle. The free acidity was high (75mN). He was then treated with the milk-soda drip. He lost the symptoms in twenty-four hours and the niche disappeared in three weeks. He remained well for three years. A slight recurrence, with negative x-rays, was relieved by one week of drip therapy. He has remained well for two years.

CASE 5.—A. Z. was a woman, aged 45 years. After a few weeks of severe ulcer symptoms, the patient had a severe gastric hemorrhage. She was treated with transfusions and Sippy therapy. She was well for six weeks. Then ulcer symptoms of a severe nature returned. X-rays showed a duodenal ulcer. Despite three weeks in bed on strict Sippy regime, her condition grew steadily worse. A moderate degree of pyloric obstruction appeared. She was then treated with the milk drip (without soda) for four weeks. She lost all of her symptoms and has remained well for five years.

CASE 6.—J. C., a man, aged 68 years, had ulcer symptoms for six years. For the six months before admission he was on Sippy therapy without relief. Radiographs revealed a large ulcer niche at the gastric angle. Milk-soda drip was then administered for four weeks. Radiographs then revealed an absence of the niche. He has remained well for eighteen months and has gained twenty pounds.

CASE 7.—L. B., a man, aged 57 years, had a twenty-three year ulcer history. A gastroenterostomy was done twelve years before admission for an obstructing duodenal ulcer. He remained well thereafter for eleven years. During the past year, he had severe ulcer symptoms, despite strict Sippy therapy. In fact, while on treatment, he experienced two massive hemorrhages. X-rays revealed a large jejunal ulcer opposite the stoma. He was then treated in the hospital with milk-

soda drip for two weeks and at home for four weeks. Radiographs then showed a disappearance of the niche. He has remained well to the present time (nineteen months).

CASE 8.—M. J. was a woman, aged 48 years. After three years of ulcer symptoms, radiographs revealed a prepyloric niche. The free acidity was high (70 mN). Despite four weeks of intensive, in-bed strict Sippy therapy, the symptoms continued. Vomiting and pain were excessive, especially during the night. She was then given the milk-soda drip. She lost the symptoms in two days and the niche in three weeks. She has gained eight pounds and remained well to the present (ten months).

CASE 9.—L. S., a man, aged 67 years, had ulcer symptoms for thirty years. A gastroenterostomy was performed seventeen years before admission. He remained well for sixteen years. He then developed severe ulcer symptoms and a large, penetrating jejunal ulcer was found opposite the stoma. He was treated for two months with Sippy therapy without relief. He then took the milk-soda drip for four weeks in the hospital and for four months more at home at night. Two months after the onset of the drip therapy, radiographs revealed an absence of the niche. He has remained well for nine years and has gained fifty pounds.

CASE 10.—M. S., a man, aged 44 years, had ulcer symptoms for eleven years. The symptoms became quite severe in the past four months. Despite Sippy therapy he had severe night pains. He was given twenty-four injections of histidin without result. Radiographs revealed a large ulcer niche at the incisura angularis. The free acidity was high (60mN). He was then given the milk-soda drip for four weeks. Radiographs then showed that the niche had disappeared. He has remained well to the present (seventeen months).

CASE 11.—G. R. was a man aged 38 years. After one year of typical ulcer symptoms, the patient experienced a severe hemorrhage from a duodenal ulcer. The symptoms continued despite six weeks of Sippy therapy. He was then treated with the milk-soda drip for three weeks. He lost the symptoms in twenty-four hours. He continued the drip at home for another three weeks. Radiographs which had revealed just before the drip therapy a tiny, deformed bulb, now showed an almost complete bulb. He has remained well for three and one-half years.

SUMMARY AND CONCLUSIONS

1. The chief point of attack in peptic ulcer therapy is the "acid-pepsin" factor.
2. The usual forms of ulcer therapy, including the Sippy method, are reviewed and their inadequacies are discussed.
3. The principles of the intragastric drip therapy for peptic ulcer are described.
4. A group of sixty ulcer patients, refractory to the usual medical therapy, were treated with milk-soda or aluminum gel by the intragastric drip procedure. Twenty-two of these are presented as examples of the successful application of this form of therapy to refractory peptic ulcer patients.

REFERENCES

1. Hollander, Franklin: What Constitutes Effective Neutralization of Gastric Contents? *Am. J. Digest. Dis.* 6: 127, 1939.
2. Winkelstein, Asher: Studies in Gastric Secretion During the Night With a Preliminary Note on a New Therapy for Peptic Ulcer, *Am. J. Surg.* 15: 523-524, 1932.
3. Winkelstein, Asher: One Hundred and Sixty-Nine Studies in Gastric Secretion During the Night, *Am. J. Digest. Dis.* 1: 778-782, 1935.
4. Cornell, Albert, Winkelstein, Asher, and Hollander, Franklin: Nocturnal Secretion Studies in Normals and in Patients With Peptic Ulcer, *Bull. New York Acad. Med.* 20: 413, 1944.

5. Woldman, E. E., and Rowland, V. C.: A New Technique for the Continuous Control of Acidity in Peptic Ulcer by the Aluminum Hydroxide Drip, *Am. J. Digest. Dis.* 2: 733-736, 1936.
6. Cornell, Albert, Hollander, Franklin, and Winkelstein, Asher: The Efficacy of the Drip Method in the Reduction of Gastric Acidity, *Am. J. Digest. Dis.* 9: 332-338, 1942.
7. Cornell, Albert, and Hollander, Franklin: An Improved Continuous Drip Apparatus With Special Reference to the Use of Alumina Gels in the Therapy of Peptic Ulcer, *Rev. Gastroenterol.* 9: 354-358, 1942.
8. Woldman, E. E.: A Collapsible Indwelling Nasogastric Tube, *Am. J. Digest. Dis.* 4: 428-429, 1937.
9. Winkelstein, Asher, Cornell, Albert, and Hollander, Franklin: Intra-gastric Drip Therapy for Peptic Ulcer—A Summary of Ten Years' Experience, *J. A. M. A.* 120: 743-745, 1942.
10. Year Book of General Medicine, Chicago, 1943, The Year Book Publishers, Inc., page 632.

THE TREATMENT OF PERFORATED DUODENAL ULCERS

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IN A former communication¹ were presented the details of the management of a series of fifty-one consecutive patients with perforated duodenal ulcers who had been admitted to the First Surgical Division of the Toronto General Hospital. The present communication includes this group together with a further series totaling 114 consecutive patients admitted to the same surgical service over a period of fifteen years since July 1, 1929. We wish to stress that this communication deals with perforated duodenal ulcers, and excludes from consideration perforated gastric ulcers. This we consider wise for two reasons: first, the number of perforated gastric ulcers which we have had the opportunity to treat has been very small, and second, a considerable proportion of these were malignant. It was felt that their inclusion in this study would but confuse the problem. We propose to confine our presentation of the management of the emergency created by the perforation of a duodenal ulcer, leaving the subsequent fate of the patient for a further communication.

All but three of the 114 patients in this series were submitted to operation. There were ten deaths. All three patients not operated upon died. Of these three, one patient refused operation. The second patient refused, and later consented, but died in the operating room before surgery could be undertaken. We failed to make a diagnosis in the third patient until the autopsy was performed. This showed a perforation of the duodenum which had localized as a left subphrenic abscess, with the terminal factor being a rupture into the bronchus. The patient drowned in his own pus.

There were seven operative deaths in 111 operations, a mortality of 6.3 per cent. There were forty-nine consecutive operations without a death. The fiftieth patient died of a pulmonary embolus on the twelfth

Received for publication, Sept. 8, 1944.

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TABLE I

Total cases perforated duodenal ulcer	114	Died 10
Total cases operated upon	111	Died 7 (6.3%)
Cause of death in three nonoperated patients		
2 refused operation		
1 undiagnosed (perforated a subphrenic abscess into bronchus)		
Cause of death in 111 patients operated upon		
1 pulmonary embolus		
1 pneumonia		
1 pneumonia with senility		
1 pneumonia with mild peritonitis		
1 uremia		
1 unrecognized pelvic abscess which perforated into the general peritoneal cavity		
1 subphrenic abscess ruptured into bronchus		

day after operation. The second death was due to pneumonia. At autopsy the abdomen was free from infection. The third patient died from pneumonia and at autopsy there was a mild peritonitis with no leak from the site of the omental patch. It was felt that pneumonia was the major factor in the mortality. The fourth patient, on the twelfth postoperative day, developed uremia and died from this cause. The fifth patient died from an unrecognized pelvic abscess, which ruptured into the general peritoneal cavity. The sixth patient died from a subphrenic abscess which was unrecognized postoperatively until it ruptured into the bronchus. The seventh patient, a senile man who could not be kept in bed, developed pneumonia and died from this cause three weeks postoperatively. He had recovered from the operation.

The ratio of males to females is striking, there being 107 male as opposed to 7 female patients in this group. Sixty-four patients were under and fifty were over 50 years of age. There were as many deaths in patients under as over 50 years of age. We cannot, therefore, consider the age of the patient as being a very important factor in determining the incidence or mortality of this emergency. The age of the patients varied from 16 to 83 years. The average age of the whole group of patients was 47 years.

Most of these patients were operated upon by the resident surgeon or the senior intern. Fortunately, the interval between the onset of symptoms and the operation has been quite short in most instances. This reflects very admirably on the efficiency of the general practitioner in this area, and furthermore it shows the wisdom of not transporting over long distances patients suspected of having a perforation. The best surgeon to operate upon a patient with a perforated duodenal ulcer is the surgeon on the spot. In no case in which we have operated has the patient made a journey longer than twenty-five miles. This was at variance with the experience in a similar group of cases in one of our Veterans' Hospitals, where the patients have been transported long distances before operation was undertaken, with a much higher mortality.

The diagnosis in most instances has presented very little difficulty. The commonest mistakes which we have made have been to diagnose erroneously as an acute perforation of a duodenal ulcer, cases of acute appendicitis, acute hemorrhagic pancreatitis, and, on a rare occasion,

acute cholecystitis. We have very rarely made a diagnosis of a perforated ulcer when the patient actually had acute appendicitis. We have had patients admitted with the diagnosis of a perforated duodenal ulcer who were proved to be suffering from coronary thrombosis. To date we have not submitted to operation any patient with the diagnosis of a perforated duodenal ulcer who was subsequently found to have a coronary occlusion. The diagnosis of a perforated duodenal ulcer in the female must always be made after very careful consideration, since it occurs so infrequently that all other possible diagnoses should be carefully assessed before concluding that the patient has this lesion. This incidence parallels the rarity of calculus cholecystitis in the unmarried nulliparous female.

In the vast majority of this group there was a previous history of indigestion, and in the patients who had this previous history there was almost invariably a history of an acute recent exacerbation of the symptoms varying in length from a few days to two or three weeks prior to perforation. There were a few cases in which it was impossible to elicit a previous history of duodenal type of gastrointestinal distress. In this group of patients the findings at operation were different from those of the group who presented a history of prolonged indigestion. There was found to be little scarring, the ulcer often presenting a punched-out appearance with very minor periperforation induration. Such we believe to result from an acute ulcer, possibly metastatic from remote infection.

The physical examination is of tremendous importance in making the diagnosis. One of us² previously outlined a trinity of symptoms regarded as indicative of an intraperitoneal catastrophe. These are: (1) the association of abdominal pain with tenderness, (2) one point of maximum tenderness, and (3) increase of pain on change of posture such as occurs when the patient rolls over in bed. In other words, if a patient complains of pain in the right iliac fossa and is tender in the area where the pain is felt, we conclude that the lesion is intraperitoneal. Such are the findings in acute appendicitis. On the other hand, if the patient complains of pain in the right iliac fossa but is not tender to palpation there, we believe the lesion is extraperitoneal, such as a ureteral stone producing colic. If one adds to this trinity the presence of rebound tenderness on abdominal examination, we accept this as irrefutable evidence of an intraperitoneal catastrophe, demanding a laparotomy.

We have never seen a case of perforated duodenal ulcer without a leucocytosis. One must recognize a physiologic leucocytosis such as may be found, for example, in the premenstrual phase in women. One must be on guard during the period of reaction from the onset of the acute pain. During this time we may find the patient reasonably comfortable with a normal temperature and a normal pulse. We may be lulled to a sense of false security and fail to recognize the emergency. Abdominal rigidity, however, is almost always present in some degree.

When the physical examination, together with the leucocyte count and urinalysis, has been carried out, the patient is taken to the x-ray laboratory and screened for the purpose of detecting the presence of air under the diaphragm. This finding is of great diagnostic value. If one

can demonstrate the presence of free air in the peritoneal cavity, it is pathognomonic of an intraperitoneal perforation. We must not, however, diagnose the presence of free air in the peritoneal cavity solely on the absence of liver dullness. We have seen instances in which the liver dullness was obliterated by distended colon. Thus, while the finding of air under the diaphragm and the absence of liver dullness are of tremendous value in diagnosis of a perforated duodenal ulcer, failure to obtain these signs conversely is definitely no deterrent to this diagnosis. Indeed, in no instance in the last seven patients with perforated ulcer which we operated upon was air demonstrable underneath the diaphragm. Shoulder-tip pain, when present, is of real diagnostic value, as it indicates diaphragmatic irritation from some cause.

Having established the diagnosis, we must ask ourselves several questions. First, why is the patient with the acute perforation of a duodenal ulcer sick? The answer to this question which would be given by many, and indeed which we believed for some time, was, that bacterial peritonitis was the factor responsible for the patient's illness. This, however, has been refuted by our studies of bacteriology of the peritoneal exudate in these patients. In fifty-nine patients cultures were taken from the peritoneal cavity at the time of operation. Thirty-four of these fifty-nine cultures yielded no growth. Of the twenty-five which showed organisms on culture, there was one instance of pure culture of typhoid bacilli in a patient who twenty years previously had suffered from typhoid fever.³ There were only two instances in which colon bacilli grew on culture. There was only one case in which there was a growth of hemolytic streptococci. This occurred in a 49-year-old man with a twelve-hour perforation, who had a perfectly uneventful convalescence and whose peritoneal cavity was closed without a drain. The other instances in which a positive culture was found included non-pathogenic organisms such as nonhemolytic streptococci, streptococcus viridans, diphtheroid bacilli, and staphylococcus albus, the latter probably being a contamination. We must, therefore, look farther afield than the peritonitis which accompanies this emergency to explain why these patients are sick. In consideration of this problem we concluded that the seriousness of the patient's emergency was in direct ratio to: (1) the degree and duration of his pain, (2) the extent of his biochemical imbalance, and (3) the degree of nutritional disturbance present.

As was mentioned before, in the great majority of these patients there had been a previous history of indigestion with a recent acute exacerbation of their symptoms. Many of them had an inadequate nutrition of long standing for one of three reasons: First, they would not eat a proper diet because of some erroneous preconceived idea; second, they were unable to retain it; third, they were never properly advised regarding the necessity and details of an adequate diet. We have been very impressed with the soundness of the conception that the nutritional disturbance of the patient at the time of the perforation is a very important factor in contributing to the seriousness of their emergency. The aphorism which has been so often quoted that, "The sun must never rise and the sun must never set on a patient suffering from an acute perforation of a duodenal ulcer without such a patient being operated upon," we believe to be thoroughly unsound. Our ex-

perience with this further group of patients has led us to believe more firmly in the wisdom of correcting the patient's nutritional disturbance and biochemical imbalance before operation is undertaken. This has, on occasions, occupied as long as twelve hours after the patient's admission to the hospital. We have never found such delay to be disastrous.

Case 1 is interesting in this connection.

CASE REPORT

CASE 1.—A man, aged 53 years, was admitted to the department of medicine for the investigation of an indigestion of which previous studies had failed to show evidence of organic disease. He had complained bitterly on many occasions of abdominal pain, and had had many previous operations. At 6 A.M. he suffered a sudden epigastric pain with diffuse tenderness and rigidity. He was seen in consultation six hours later. Screening showed no free air under the diaphragm. He appeared to be desperately ill, his blood pressure being 70/50. The diagnosis of a perforated viscus presented little difficulty. The condition of the man, however, was so poor that immediate operation was considered unwise. He was put in an oxygen tent, was given sufficient sedative to relieve the pain, and was given an intravenous injection of saline solution and glucose, as well as 500 c.c. of plasma and 500 c.c. of whole blood, all intravenous medication being by the drip method. His condition improved and at the end of ten hours his blood pressure was 110/76 and pulse was 80. His appearance and general condition were in marked contrast to his state when first seen. Interestingly enough at operation, which revealed a perforated duodenal ulcer, cultures from the intraperitoneal exudate were sterile. Despite the fact that operation was not undertaken until sixteen hours following the perforation, ten hours being consumed in preoperative preparation, he made an uninterrupted recovery. We are convinced that in this case immediate operation would have ended fatally.

One may ask, what are the criteria for deferring operation? This can be summed up in an assessment of the patient's general nutrition, the state of dehydration, the blood pressure, pulse rate, and temperature. We have never regretted the time consumed in the preoperative preparation of the desperately ill patient. Furthermore, in this group of 114 patients, in which there were 7 operative deaths, there were only 3 instances in which the peritoneal infection was a contributing factor to the fatality. There were two subphrenic abscesses which ruptured into the bronchus, one of which was not diagnosed until autopsy. The third patient had pneumonia with an early mild peritonitis and the pneumonia was considered to be the major factor responsible for the fatality.

The next three questions we must ask ourselves are: (1) Why is an emergency operation ever necessary in gastrointestinal disease? (2) What is the surgeon's responsibility in an emergency operation on the gastrointestinal tract? (3) Upon what do we depend for the closure of gastrointestinal perforation? These three questions must be answered in order to undertake the operative procedure intelligently and adequately.

In answering the first it must be obvious that we do an emergency operation solely because we believe that without operation the patient would die. In answering the second, the surgeon's responsibility in an emergency operation is solely to save life, and to do that with the most simple, minimal, surgical procedure which will accomplish this end. The third answer is that all gastrointestinal perforations are closed by the formation of fibrin. This makes possible all intestinal anastomoses.

The perforation made by each stitch is soon healed by fibrin. Our problem is to ensure fibrin formation at the site of the perforation.

With this conception of our responsibility in an emergency operation, we can consider the anesthetic. We are firmly convinced that the use of a spinal anesthetic is ideal. There have been instances when the patient was so desperately ill that this anesthetic seemed injudicious. With increasing experience, however, the contraindications are decreasing. We used local block anesthesia in the abdominal wall, plus splanchnic block anesthesia transperitoneally in the patients who were too ill for spinal anesthesia. The patient enters the operating room with a Levin tube in the stomach and an intravenous infusion of glucose and saline solution already running. The intravenous therapy is useful not only for immediate value, but to provide a medium whereby stimulants may be given effectively and readily should the need become urgent during the operation. We recently have been using sodium pentothal as a supplement to spinal anesthesia to overcome any apprehension and restlessness on the part of the patient.

If the diagnosis is in doubt, and it is impossible to determine whether the patient is suffering from acute appendicitis or a perforated ulcer, the peritoneal cavity is opened through a gridiron incision in the right iliac fossa. This results in a minimum trauma. If the appendix is the source of the trouble it is effectively dealt with, whereas if the appendix is normal the upper abdomen may then be opened by a separate incision. Fibrin may be present around the appendix in the right iliac fossa, although the original lesion is a perforated ulcer. One must be on guard to recognize that such is a periappendicitis and not a primary appendicitis. To be alert to this possibility is sufficient to avoid an error. In our opinion it is much less traumatic to approach the doubtful case in this manner than it is to make a more extensive paramedian laparotomy wound as the primary procedure.

If there is no doubt as to the diagnosis, the abdomen is opened through the upper right rectus muscle and the perforation usually is readily found by following the fibrin toward the duodenal cap.

Accepting the philosophy that we have no responsibility except to save the patient's life, we are spared any debate as to whether we should do a concomitant gastrojejunostomy, pyloroplasty, or gastric resection. None of these procedures is necessary to save the patient's life. Some may argue during the operation for acute perforation that the degree of scarring and induration at the site of the perforation makes pyloric obstruction inevitable. The operative procedure we suggest will not add to the mechanical obstruction which antedated the perforation. The patient presented no emergency problem because of pyloric obstruction prior to the perforation, thus any aggravation of the pyloric stenosis is due to edema resulting from the acute inflammatory process accompanying the perforation. This can be controlled by using an indwelling duodenal tube with Wangenstein suction, maintaining by parenteral means adequate nutritional and biochemical balance. In the few cases in which this proves inadequate, a jejunostomy may be simply and safely done as an operation of election. This permits complete study of the patient and the performance of an adequate gastric operation at the optimum time. We cannot too heartily condemn all procedures save simple closure at the operation for the acute perforation.

We have at this time no responsibility whatsoever to attempt to cure the patient of his duodenal ulcer. Realizing also that fibrin is responsible for the closure of all perforations in the gastrointestinal tract, we guide fibrin to the perforation in the most simple manner possible. Three interrupted catgut sutures are placed parallel to the long axis of the duodenum, one above, one below, and one across the perforation (Fig. 1). We then lay over the perforation a piece of omentum, either attached or detached, whichever seems the less disturbing to the intraperitoneal content, and then tie the sutures just sufficiently tight to hold the omental patch in position (Fig. 2). The sutures are not tied tight enough for an attempt to be made to close the perforation. They

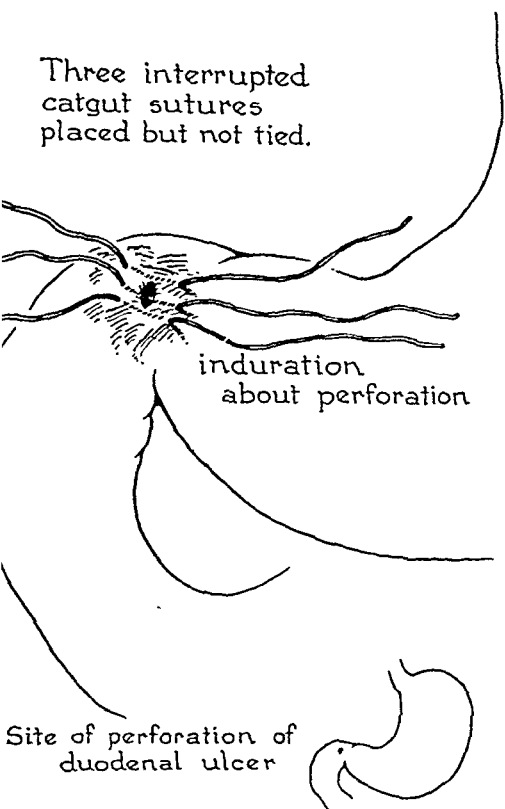


Fig. 1.

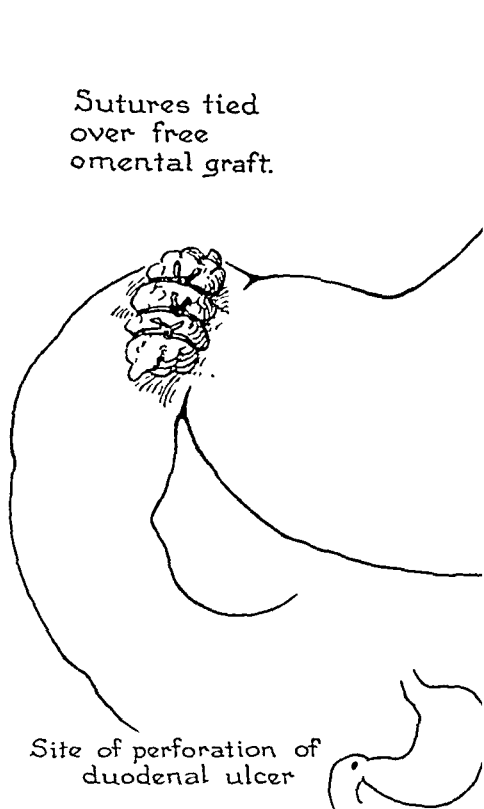


Fig. 2.

Fig. 1.—The placing of sutures in relation to perforation.

Fig. 2.—Sutures tied over free omental graft. No attempt is made to close the perforation by the sutures. They are tied only sufficiently tight to hold the graft in situ.

simply hold the omentum over the perforation so that fibrin forms in this area. If there is gross soiling of the peritoneal cavity, the exudate is sucked out, but one should not be so insistent upon sucking out all the intraperitoneal fluid as to traumatize the intraperitoneal contents unnecessarily. The abdominal wall is then closed without drainage, according to one's practice. Closure with stainless steel wire as advocated by Jones and associates⁴ we believe is admirable. The elimination of drainage has become almost routine. Unless there is gross contamination in a very late perforation it serves no useful purpose. In ninety-eight cases in which the presence or absence of drainage was definitely stated, a drain was left in at the time of the original operation in only fourteen. We have not used any of the sulfonamide drugs rou-

tinely in the peritoneal cavity. In this entire group there were only three cases in which a sulfonamide was left in the peritoneal cavity.

On the patient's return to the ward, if his condition is grave, he is placed in an oxygen tent and given sufficient sedative, preferably morphine, to control his pain. The intravenous administration of saline solution and glucose is maintained, and the stomach is kept empty by aspiration of the indwelling duodenal tube. We then carry on with the postoperative routine suggested by one of us⁵ for gastric operations. The patient's position is changed every two hours and he is encouraged to exercise the legs. Overbreathing is stimulated by the administration of carbon dioxide every two to four hours for the first twelve hours postoperatively and he is encouraged to cough.

If the patient is not doing well, there are three areas which must be examined immediately: first, the chest; second, the subphrenic spaces; and third, rectal. A rectal examination would have avoided the disaster which occurred to us when an unrecognized pelvic abscess perforated into the general peritoneal cavity and caused a fatality. There is one pitfall in the investigation of the subphrenic spaces. If the patient has been operated upon under spinal anesthesia, and his unsatisfactory postoperative course leads one to suspect the presence of a subphrenic abscess, x-ray studies which show free gas under the diaphragm must not be taken as evidence in the support of a subphrenic lesion. Lewis⁶ has shown in a series of cases that air will normally occupy the subphrenic space in patients who have had a laparotomy under spinal anesthesia for as long as six weeks following operation. In our hospital, as reported by Doidge and Warner,⁷ the diagnosis of a subphrenic abscess requires all the resources at our disposal and despite these we fail all too frequently.

Before the patient is discharged from the hospital a careful survey is made for possible sources of infection in the teeth, tonsils, and accessory sinuses. Advice is given, in writing, detailing the management of his life and diet. We believe it is much more important for a patient to eat a varied diet between meals and at bedtime, as well as the three main meals, than it is to go on any elaborate and detailed and curtailed diet. We also insist on the value of avoiding the use of alcohol or tobacco in any form.

A further communication will deal with the subsequent fate of these patients, the incidence of postoperative symptoms, and the necessity for subsequent operation.

SUMMARY AND CONCLUSIONS

1. A series of 114 perforated duodenal ulcers is presented. One hundred and eleven patients were operated upon with seven operative deaths, a mortality of 6.3 per cent. In only three patients did an intraperitoneal infection contribute to the fatality.

2. The factors responsible for the seriousness of this emergency are: (a) the degree and duration of the pain, (b) the degree of biochemical imbalance, and (c) the degree of nutritional disturbance.

3. The preoperative treatment of the patient is the most important factor in lowering the operative mortality, despite the necessity of deferring the operation on occasion for as long as twelve hours.

4. Bacterial peritonitis as a factor in the seriousness of this emergency is a late manifestation. In fifty-nine cultures, thirty-four were sterile. In only two cases were colon bacilli found on culture. Hemolytic streptococcus was recovered once and a pure culture of typhoid once. The other positive cultures contained nonpathogenic organisms. These findings justify withholding operation while biochemical and nutritional disturbances are corrected.

5. The routine use of sulfonamide drugs intraperitoneally appears superfluous.

6. Drainage of the abdomen at the time of closure of the perforation is unnecessary.

7. Under spinal anesthesia the closure of the perforation by an omental patch, attached or detached, held in place by three interrupted catgut sutures is an efficient and simple method. This reduces operative trauma and technical difficulties to the minimum and can be carried out with safety despite limited facilities.

REFERENCES

1. Graham, R. R.: Treatment of Perforated Duodenal Ulcers, Surg., Gynec. & Obst. 64: 235-238, 1937.
2. Graham, R. R.: Surgical Emergencies in General Practice Exclusive of Trauma, Canad. M. A. J. 34: 36-40, 1936.
3. Clifford, E. J.: Perforated Duodenal Ulcer in Typhoid Carrier, Canad. M. A. J. 28: 194-195, 1933.
4. Jones, T. E., Newell, E. T., Jr., and Brubaker, R. E.: The Use of Alloy Steel Wire in the Closure of Abdominal Wounds, Surg., Gynec. & Obst. 72: 1056-1059, 1941.
5. Graham, R. R.: Technical Surgical Procedures for Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. 66: 269-287, 1938.
6. Lewis, F. I.: Pneumo-peritoneum Following Laparotomy, Canad. M. A. J. 28: 18-23, 1933.
7. Doidge, W. A., and Warner, W. P.: Subphrenic Abscess, SURGERY 4: 405-414, 1938.

EXPERIMENTAL EVALUATION OF A SATISFACTORY OPERATION FOR ULCER

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INTRODUCTION

I. Purpose of the Present Study

OF ALL the theories that have been advanced regarding the etiology of ulcer, the majority of investigators now recognize acid as the most important single factor. Whereas it has been known for some time that ulcer might be produced by various surgical procedures which alter the normal anatomy, only recently has it been possible to produce

The researches presented here were supported by grants of the Citizens Aid Society, and the Augustus L. Searle Fund for Experimental Surgical Research.

*In partial fulfillment of the requirements for the degree of Doctor of Philosophy, May, 1944.

typical chronic duodenal and gastric ulcers in a variety of intact laboratory animals.

It thus becomes apparent that an operative procedure, which would protect an animal against the development of such an experimentally induced ulcer, would have considerable clinical value in the surgical therapy of ulcer in man where similar lesions occur spontaneously.

It is the purpose of this study then, to evaluate several operative procedures, experimentally, and determine which one or ones would have satisfactory clinical application.

II. Review of the Literature

The voluminous accumulated literature attests to the widespread interest which the ulcer problem has initiated.

Countless means and methods have been employed in an attempt to reproduce the clinical lesions in experimental animals.

It should be stated initially that the difference between the acute and chronic ulcer has long been appreciated. Morton⁸³ stated that, "the means of inducing chronic ulcer in animals, experimentally, are as few as those of inducing acute ulcer are numerous." Whereas an acute ulcer may be produced by a variety of methods, almost invariably it is found to be entirely healed within two or three weeks. It was not until the work of Mann and Williamson⁷⁶ (1923) that a method was made available of producing chronic ulcers consistently in a high percentage of animals.

Although, as has been mentioned, the methods previously employed have been quite numerous and varied, an attempt will be made to classify them, give examples of each group, and discuss a few of them somewhat more in detail.

A. Methods Altering the Normal Anatomy and Physiology of the Alimentary Tract, Especially the Normal Capacity for Neutralization, the Chemical Factor.—Bickel¹⁰ (1909) excised the duodenum in two dogs and established continuity by gastrojejunostomy. He implanted the bile and pancreatic ducts into the abdominal wall as external fistulas. At autopsy, after four and one-half weeks, one of the animals showed several jejunal ulcers, one of which perforated with resulting peritonitis and death. Exalto³⁵ (1911) observed no ulcer in seven dogs with gastroenterostomy. However, of seven dogs upon whom the Roux Y operation was performed, six subsequently developed ulcer. He stated that jejunal ulcers were due to the action of the acid gastric juice on the intestinal mucosa. Because of his findings, he condemned the Roux Y operation and indicated that the operation least likely to be followed by jejunal ulcer was a posterior gastroenterostomy performed as close as possible to the duodenum. These observations were quite remarkable as they are certainly true today, nearly thirty-five years later.

Grey⁴² (1919) performed duodenectomy in dogs in multiple stages. At the first stage the common bile duct was ligated and the gall bladder anastomosed to the proximal jejunum. At the second stage, the major pancreatic duct was transplanted into the proximal jejunum and finally the duodenum was resected and the upper jejunum was anastomosed to the stomach. However, of four animals surviving the

second stage, two subsequently died before the final procedure could be accomplished. At autopsy, both animals were found to have perforated peptic ulcers—one in the distal duodenum and the other in the first inch of jejunum, above the transplanted pancreatic duct. He concluded that the ulcers were due to the absence of the strongly alkaline juices ordinarily present in this region.

Mann and Kawamura⁷⁵ (1922) studied the effects of duodenectomy. Of ten animals coming to necropsy, two showed typical jejunal ulcers. The following year (1923) Mann and Williamson⁷⁶ described their operation of "surgical duodenal drainage" in which the alkaline duodenal secretions are shunted into the terminal ileum. Fourteen of sixteen dogs developed typical subacute or chronic jejunal ulcers. Mann ascribed this occurrence to a chemical and a mechanical component. He emphasized the significance of unneutralized gastric acid and the "nozzlelike" action of the pylorus which allowed the gastric secretion to come in contact with the duodenal mucosa in spurts with considerable force.

Mann and Williamson's work was widely recognized and confirmed by a number of investigators. Following this, numerous studies were undertaken to determine which of the duodenal secretions, the bile, pancreatic juice, or succus entericus provided the greatest neutralizing capacity for the acid gastric juice.

Dott and Lim²⁹ (1923) noted typical jejunal ulcers in dogs after gastroenterostomy with pyloric exclusion as suggested by Von Eiselsberg,¹⁰⁹ but did not note them in gastroenterostomy without pyloric exclusion. They therefore concluded that acid chyme was necessary to stimulate the alkaline secretions of the duodenum including the bile and pancreatic juice, and that with deficient alkaline secretion, ulcer would result. These findings are quite interesting and will be discussed later, somewhat more in detail.

Dragstedt and Vaughn³⁰ (1924) attempted to answer the age-old question of "why the stomach does not digest itself." They implanted various segments of intestine, spleen, and kidney into the stomach but failed to note any evidences of digestion. They concluded that the immunity to resist gastric digestion was more general than was formerly supposed and did not reside wholly in mucous membranes. They suggested that the hypothesis that all living uninjured cells could resist digestion was partly true.

Kapsinow⁵⁸ (1926) accomplished total exclusion of bile by ligating the common duct and performing cholecystonephrostomy. He succeeded in producing typical duodenal ulcer in seventeen of forty-three animals and, therefore, concluded that bile was an important factor in neutralization.

De Takats and Mann²⁶ (1927) transplanted 5 cm. jejunal loops and sutured them as patches into the stomach wall. A typical peptic ulcer occurred in three of twenty-five animals when the patch was placed along the lesser curvature; they did not occur if the patches were placed elsewhere in the stomach. They felt that this finding added significance to the mechanical factor in the formation of ulcer.

Morton⁸³ (1927) confirmed the findings of de Takats and Mann and continued the investigation. He produced acute ulcers in the stomach

by excising segments of the mucosa and submucosa and noted that all healed in normal fashion. He then excised small areas of the mucosa and performed the Mann-Williamson operation coincidentally. A delay in healing resulted in all experiments, and 50 per cent of the ulcers on the lesser curvature became subacute or chronic, whereas similar areas on the greater curvature healed.

In another series of experiments he performed the duodenal drainage operation. After an interval of twenty to sixty-five days, the animal was again operated upon and the presence of a jejunal ulcer confirmed. A gastroenterostomy was performed at this laparotomy. The animals were then sacrificed in from four to sixteen days. All ulcers showed unmistakable evidences of healing. However, newly developing ulcers were found opposite the gastroenteric stoma.

Somewhat later Morton⁸⁴ placed jejunal patches in various locations on the stomach, as suggested by Mann, and noted only one ulcer. He then did the operation of duodenal drainage in thirteen animals. Of five dogs with the patches on the lesser curvature, typical ulcer developed in three instances. Otherwise, no ulcer occurred and it thus appeared that the lesser curvature was the most susceptible location.

McCann⁶⁹ (1929) altered the Mann-Williamson operation by implanting the duodenal loop high in the fundus of the stomach, thus assuring complete intragastric regurgitation. Jejunal ulcers were found in 80 per cent of twenty-six dogs following this procedure. He also studied the gastric secretion following the procedure and the Mann-Williamson operation. No significant change in the acidity of the secretion resulted and he therefore assumed that the jejunal ulceration was due to a failure of neutralization of the normal acid chyme rather than a hyperacid secretion.

Neuman, Demoor, and Deloyers⁸⁵ (1931) noted ulcers in four of seven dogs with total exclusion of bile into the terminal ileum. With deviation of duodenal and pancreatic secretions, ulcers were obtained in two of six dogs. Loewy⁶⁸ also produced duodenitis and ulceration with total external biliary fistulas. Berg and Jobling⁸ (1930) noted chronic duodenal ulcers in thirteen of twenty-three dogs with various types of biliary exclusion.

Elman and Hartmann²³ (1931), however, emphasized the importance of the pancreatic juice and noted ulcers in six dogs with pancreatic fistulas which drained for thirteen days or more. Berg and Zucker⁹ (1932) again, on the contrary, re-emphasized the importance of the bile and noted ulcers in 60 per cent of animals with biliary exclusion and only one ulcer in fourteen animals with pancreatic fistula. In a later report, Berg⁷ (1934) found only one ulcer in sixteen dogs with pancreatic fistula, and no ulcers in eight dogs with total pancreatectomy.

Owings and Smith^{90, 91} (1932) also favored the bile as the most important neutralizing factor in preventing ulcer. They performed Mann-Williamson operations but implanted the duodenal loop only twenty-four inches below the gastroenterostomy which had been made a few inches below the ligament of Treitz. In seven dogs in which ulcer developed, they then implanted the proximal loop into the stomach; in four instances the ulcer healed completely, and in two cases partial healing resulted. This would appear to be contrary to McCann's findings.

Jenkins and Palmer⁵⁴ (1931) performed Mann-Williamson operations but made a wide side-to-side gastroenterostomy stoma rather than the usual end-to-end gastrojejunostomy. The same incidence of ulcer resulted, however, and they therefore concluded that unneutralized acid was the most important factor rather than the mechanical effect. Later, Gallagher and Palmer⁴⁰ (1933) noted no difference in the rate of development of jejunal ulcer in the Mann-Williamson preparation if the duodenal loop was implanted at various levels in the intestinal tract.

Bollman and Mann¹² (1932) found ulcer in sixty-four of eighty-seven dogs with ligation of the common bile duct and Kim and Ivy⁶⁰ (1931) noted spontaneous duodenal ulcers in six of ten dogs with biliary fistula.

Mann and Bollman⁷³ (1932) were able to produce ulcer by dripping 0.4 per cent hydrochloric acid into the stomach through an intestinal fistula and stated that daily repetition of excess acidity was necessary to cause a depression of neutralization.

In a preliminary report, Matthews⁷⁸ (1931) noted the effect of anastomosing a Pavlov pouch to an isolated loop of lower ileum. A typical ulcer developed in all instances (six dogs) within eighty days.

Matthews and Dragstedt⁷⁹ (1932) furnished considerable evidence for the acid genesis of ulcer. They stated that the results of Dragstedt and Vaughn³⁰ might be explained by the neutralizing effect of food, swallowed saliva, mucus, and the regurgitation of alkaline duodenal juices. Their "experimental Meckel's diverticulum ulcer" demonstrated convincingly the corrosive chemical action of unneutralized pure gastric juice. They also repeated the Mann-Williamson experiment but implanted the duodenal loop only 40 cm. below the gastrojejunostomy.

Only one ulcer in twenty-one experiments was noted. They then introduced a valve which prevented regurgitation of the duodenal juices, and chronic jejunal ulcers resulted in six cases.

Similarly, the prevention of the regurgitation of the alkaline duodenal juices into the stomach of normal dogs by the introduction of a valve into the pylorus raised the free and total acidity of the gastric content, delayed healing of acute gastric ulcers, and caused the appearance of spontaneous ulcers in intestinal mucosal transplants.

Harper^{45, 46} (1932 and 1935) attacked the problem in a slightly different manner but with convincing results. He made fundic pouches in the dog and used antiperistaltic loops of various segments of the intestine to carry the secretion to the outside as described by Mann and Bollman.⁷⁴ He found that ulcers formed in the fistulas in all instances. The average interval before perforation when utilizing the ileum was twenty-three days, whereas, with the jejunum the interval increased to seventy-one days. If the duodenum was employed, ulcers developed but perforation did not occur. He thus concluded that the upper intestine is more resistant to the corrosive action of gastric juice than the lower segments. If catheters were introduced through the fistulas into the pouch to assure good drainage, ulceration failed to occur.

Ivy, Schrager, and Morgan⁵³ noted spontaneous duodenal ulcers in dogs with chronic mild icterus and hepatitis.

Hoerner⁴⁹ (1934) studied the effect of exclusion of the pancreatic juice from the duodenum. Following evulsion of the pancreatic ducts, ulcer failed to occur, but with pancreatic fistula, ulcer was observed in 42 per cent of the animals.

No change in the gastric contents was found following either of these procedures but the reaction of the duodenal contents in a fasting state was more variable and after a protein or carbohydrate meal the pH of the duodenal content was lower and maintained for a longer time.

Ochsner, Gage, and Hosoi⁸⁷ (1934) convincingly demonstrated the protective influence of bile. They noted an incidence of ulcer in 85 per cent of animals in whom pouches had been anastomosed to the jejunum. However, if the bile was introduced by anastomosis of the gall bladder to the pouch, the incidence of ulcer was lowered to 39 per cent.

Blanch¹¹ (1935) believed that the loss of bile was of paramount importance in inducing experimental ulceration. He made complete external biliary fistulas in eight dogs. Five were fed only the stock diet and all developed ulcers. The remaining three were fed the bile collected from the biliary fistulas in addition to the stock diet and no ulcers were observed.

Wu¹²² (1935) made Mann-Bollman fistulas 5 to 10 cm. below the ligament of Treitz and studied the pH of the intestinal content. He then performed the Mann-Williamson operation and observed that the jejunal contents were much more acid than normal, and subject to wider fluctuations. McMaster⁷¹ (1934) made end-to-side anastomosis between the pyloric end of the stomach and progressively lower levels of the intestine from the duodenum to the colon. The intestinal mucosa was observed to be increasingly sensitive to gastric content from the duodenum to the colon. No ulcers were observed with gastroduodenostomy, a 45 per cent incidence with gastrojejunostomy, an 80 per cent incidence with gastroileostomy, and a 100 per cent incidence with gastrocolostomy. He believed the acid gastric content appeared to be the most important factor in the production of ulceration of the intestinal mucosa. These findings offer opportunity for considerable speculation and will be discussed more in detail later.

DeBakey²⁵ (1937) attempted to ascertain the relative protective power of the bile, pancreatic juice, and succus entericus. He performed pyloric exclusion and gastrojejunostomy after the method of Von Eiselsberg.¹⁰⁹ He then excluded the bile and pancreatic juice individually and collectively.

With pyloric exclusion alone, ulcer was observed in 50 per cent of the animals; with pancreatic juice excluded, 70 per cent; with bile excluded, 90 per cent; and with both juices excluded, 100 per cent. He, therefore, concluded that bile was of greatest importance in preventing the formation of jejunal ulcer, with pancreatic juice next in order and the succus entericus least important.

Bachrach, Schmidt, and Beazell¹ (1939) observed only two ulcers in fifteen dogs with complete biliary fistulas if the collected bile were returned. In nineteen dogs with pancreas separated from the duodenum, only one ulcer was observed.

Schiffirin⁹⁶ (1940) stressed the importance of pepsin and was unable to produce ulcer in an intestinal loop by employing acid alone but succeeded with an acid pepsin mixture.

However, Walpole and his co-workers¹¹⁰ produced ulcer in the cat by instillation of dilute hydrochloric acid, and Varco¹⁰⁷ succeeded in producing ulcer in a loop of dog's intestine employing acid.

More recently Kolouch,⁶¹ by observing directly the effects of acid on an exposed loop of intestine, has studied the pH necessary to produce ulceration.

In summary, several facts become apparent. The effect of unneutralized gastric acid is undeniable. Mechanical and traumatic factors may play a role but certainly a lesser one. Bile appears to be the most important factor in neutralizing acid, with pancreatic juice next in order and the succus entericus least important. Ulcer may be produced consistently by altering the normal acid-alkaline mechanism. There appears to be a progressive increase in susceptibility to gastric acid from the duodenum to the colon.

B. Methods Altering the Normal Vascular Supply of the Stomach.—Virchow's theory of embolic infarction as the etiologic agent in ulcer stimulated many investigators to attempt to produce ulcer disturbing the normal blood supply to the stomach. The first attempts were the introduction of foreign body particles into the blood stream.

Panum⁹² (1862) injected an emulsion of wax into the femoral artery of dogs and produced multiple hemorrhagic infarcts and ulcers in the stomach. However, the majority of the animals died within twenty-four hours, so the fate of the ulcers was inconclusive. Cohnheim²¹ (1890) injected a suspension of lead chromate into one of the gastric branches of the splenic artery. He produced large ulcers which were usually perfectly healed at the end of three weeks. Other investigators used a variety of substances with rather variable results. Ivy⁵² injected suspensions of finely divided animal charcoal into the gastropiploic arteries with negative results, but succeeded in producing acute ulcers in three animals by using lead chromate.

The effects of ligation of blood vessels supplying the stomach were also investigated. Litthauer⁶⁶ was able to ligate the blood supply of one-third of the stomach without producing ulcer. He then ligated all the vessels in a given area of the stomach, excised a segment of mucosa, and fed the animals 200 c.c. of dilute hydrochloric acid daily. He was able to produce ulcer in two of eight experiments but stated that the "artificial production of a condition of hyperchlorhydria was essential to obtain a true gastric ulcer."

Ivy⁵² ligated six to eight of the branches of the gastropiploic vessels supplying the pyloric portion of the stomach, with negative results. He also made silver nitrate ulcers in areas where the large blood vessels had been ligated and found that they healed in normal time.

Reeves⁹⁴ studied the anatomic arrangements of the arteries along the lesser curvature and first portion of the duodenum and noted that anastomoses were infrequent. He suggested that these vessels were predisposed to thrombosis which might be an important factor in the causation of ulcer by hematogenous infection.

Layne and Bergh⁶⁴ found that ligation of two or three of the large arteries supplying the stomach produced no significant alteration of acid gastric secretion nor alteration in the appearance of the gastric mucosa. Thus it would appear that alterations in blood supply to the

stomach, which might occur clinically, would be distinctly unusual and most certainly play a minor role as etiologic factors in the production of ulcer.

C. Methods Altering the Normal Nerve Pathways.—A number of investigators have altered the normal nerve pathways in an attempt to produce ulcer. The majority of attacks have been directed at the vagi, the splanchnics, and the central nervous system. Unfortunately, a number of conflicting reports have caused some confusion in this regard, especially the vagi.

Duranto³¹ (1916) produced ulcer by resecting the splanchnic nerves. He stated that the integrity of the gastric cell was dependent upon the sympathetic nervous system and damage to these structures would cause a "trophic" ulcer. Greggio⁴¹ (1916) was able to produce ulcer in the dog and rabbit by vagotomy. Beaver and Mann⁵ (1931) made Mann-Williamson preparations and, in addition, sectioned the vagi in the thorax in one series of animals, and in another, divided the splanchnics. Ulcer developed in all except one instance and they, therefore, concluded that section of these nerves would not prevent the occurrence of ulcer.

Beazell and Ivy⁶ found gastric ulcer in twelve of twenty-nine rabbits fed on a rough diet and in whom bilateral vagotomy had been performed. If the animals were fed a soft diet, however, ulcer was observed in only three of nineteen animals. They concluded that mechanical trauma was a factor, therefore. Ulcer did not occur in sixty dogs receiving a soft diet, upon whom bilateral vagotomy was performed above the diaphragm.

Lium⁶⁷ (1941) noted peptic ulcers in four of nine dogs upon whom the prevertebral ganglia had been removed.

Oberling and Kalto⁸⁶ noted, incidentally, lesions of the stomach in twelve of twenty-nine animals after operations upon the central gray nuclei.

Cushing²⁴ reported clinically three perforated ulcers following craniotomy with a fatal outcome in each instance.

It has not been possible, however, to reproduce typical gastric and duodenal lesions consistently by any of these methods and other avenues of approach appear more profitable.

D. Bacterial Methods.—Turek¹⁰³ (1906) produced ulcers in dogs by feeding *Bacillus coli communis*. However, Bauer³ (1910) was unable to confirm Turek's findings and stated that the alleged ulcers were only pseudo-ulcers which were similar to Peyer's patches. From the published photographs in Turek's paper, it would appear that Bauer was correct.

Rosenow⁹⁵ has published several papers dealing with this subject and has reported the production of gastric and duodenal ulcers which resemble those in man by the intravenous injection of alleged specific streptococci. However, Wilensky and Geist¹¹⁹ were unable to confirm Rosenow's work.

They made defects in the stomach wall of cats and implanted cultures of organisms from a human ulcer with negative results.

Ivy⁵² injected cultures of streptococci into two or three branches of the gastropiploic arteries in a series of dogs, with negative results.

Bacteria were also fed by mouth, and lacerations which had been made in the gastric mucosa healed in normal time and no ulcers developed. However, in cachectic animals, chronic ulcer was occasionally observed.

Hoffmann⁵⁰ (1925) was able to produce ulcer in guinea pigs by injecting, intra-abdominally, a solution of stomach contents from patients with ulcer. He was also able to reproduce the findings in other guinea pigs by injecting cultures taken from the induced ulcers.

It is well known that ulcer is a disease which occurs in individuals who are otherwise healthy and, in the light of our other knowledge, it seems unlikely that bacteria play a very significant role in the genesis of ulcer.

E. Methods Involving Dietary Alterations.—Kim and Ivy⁶⁰ fed neutral gastric mucin to seventeen dogs with external biliary fistula and prevented the development of ulcer.

Smith and McConkey¹⁰¹ noted ulcers in 26 per cent of guinea pigs placed on a diet deficient in vitamin C. Diets deficient in vitamins A, B, or D did not cause ulcer if the vitamin C intake was adequate.

Weech and Paige¹¹⁷ found ulcers in eight (36 per cent) of twenty-two dogs placed on a protein deficient diet. An additional 23 per cent showed erosions without true ulcer formation.

Wu¹²³ observed that subcutaneous injections of histidine would not protect animals against the development of ulcer after the Mann-Williamson operation. These observations were contrary to those of Weiss and Aron.¹¹⁸

Cheney²³ produced ulcers in chicks by deficient diets and observed hyperacidity in the chicks with ulcer.

Again, it is appreciated that ulcer occurs quite universally in people who have subsisted on a variety of diets and thus here, too, it seems unlikely that dietary alterations would play more than a minor role in the production of ulcer.

F. Methods Employing Certain Drugs.—These methods usually include the injection of a drug into an intact animal or directly into the wall of the stomach. A wide variety of drugs has been used and it is possible to produce acute ulcer with a number of different substances. Underhill and Freiheit¹⁰⁵ (1928) found that acute ulcerations could be produced in a rabbit's stomach with toxic doses of pilocarpine. They noted similar findings using a combination of pilocarpine and epinephrine but epinephrine alone would not produce the lesions. The ulcerations appeared more pronounced with an acid condition in the stomach and the pilocarpine caused a marked increase in peristalsis.

Light, Bishop, and Kendall⁶⁵ were able to produce gastric ulcers in rabbits in 94 per cent of instances by injecting only 10 mg. of pilocarpine into the lateral cerebral ventricles. A similar proportion was noted with subcutaneous administration only if the dose was increased to at least 75 mg.

Van Wagoner and Churchill¹⁰⁶ (1932) first noted gastric and duodenal ulcers in experimental cinchophen poisoning. Stalker, Bollman, and Mann¹⁰² continued the inquiry and noted that the gastric acidity was, apparently, unchanged but there was an increased secretion when the ulcer was developing. They believed the lesion started as diffuse

gastritis which developed into superficial erosions and acute ulcers which occasionally became chronic. They were able to produce the lesion in dogs by administering the drug either orally, intravenously, subcutaneously, rectally, or by injection into an intestinal fistula. Simonds¹⁰⁰ believed that cinchophen ulcers originated in areas of purulent gastritis and that hyperacidity was not a significant factor.

Dodds and co-workers²⁸ produced a lesion in the fundus of a rabbit's stomach by the injection of posterior pituitary extract. The lesion was markedly limited to the acid-bearing area, however, and was not at all similar to clinical ulcer.

Metz⁸¹ has reproduced the findings in the rabbit's stomach, but also states the lesion is in no way similar to peptic ulcer occurring in man and has, on the contrary, treated clinical ulcers using pituitary extract with encouraging results.⁸²

Hanke⁴³ noted ulcer in cats after daily injections of 2 to 3 Gm. of caffeine sodium salicylate. Kanatake⁵⁷ produced ulcer by subcutaneous administration of various aliphatic amines.

The highest incidence of positive results, however, has followed the use of histamine. The profound effect of histamine upon gastric secretion has long been appreciated.

McIlroy⁷⁰ (1928) made traumatic lesions in the prepyloric region of cats. He then injected histamine in 10 to 20 mg. doses on alternate days and noted extension of the original lesion in all except one instance. He attributed the results to the increased hydrochloric acid induced by the histamine.

Büchner and Molloy¹⁴ (1927) produced ulcer in about 33 per cent of rats, employing doses of 6 to 12 mg. histamine per 100 Gm. of body weight. Atropine in 0.5 mg. doses did not change the effect.

Büchner, Siebert, and Molloy¹⁵ (1928) continued the study and noted an increased incidence of ulcer by starving the animals on alternate days.

Bürklee-de la Camp¹⁶ (1929) enlarged upon Büchner's work. He also produced ulcer in rats by histamine injection and starvation, and observed that the results were not altered by dividing both vagi. He was, however, unable to produce ulcer in an intact dog, even combined with two to three days' starvation, but demonstrated delayed healing in artificially produced ulcers.

Matseuda⁷⁷ (1931) produced ulcers and erosions in 60 per cent of guinea pigs, 33 per cent of dogs, and 22 per cent of rabbits using doses of histamine ranging from 1 to 3 mg. per kilogram given three times daily.

O'Shaughnessy⁸⁹ (1931) noted ulcer in two of five cats by injection of a histamine solution into the muscular layer of the stomach wall. One ulcer was quite similar to a chronic ulcer in man.

Harde⁴⁴ (1932) was able to produce subacute and chronic lesions in the stomach of mice by subcutaneous injections of 0.25 mg. histamine. He noted no lesions in rabbits and only a few in guinea pigs with a dose of 1 mg. per animal.

Eppinger and Leuchtenberger³⁴ (1932) observed edema, swelling, and reddening in the gastric mucosa of the dog, following histamine injections. There were punctate and hemorrhagic erosions but no true ulcers.

Friedenwald, Feldman, and Morrison³⁹ (1933) assayed the effect of a number of substances by direct injection into the gastric wall. They employed representatives of fats, CHO, protein, metals, and other chemicals, principally various strengths of hydrochloric acid. They were able to produce only one small healed ulcer, employing histamine. Acute ulcer could be produced quite regularly by injecting 1 per cent hydrochloric acid into the stomach, and when histamine was given concurrently by subcutaneous administration, no evidences of chronicity followed. They, therefore, concluded that the prolonged administration of histamine is not a factor in the production of chronic ulcer.

Carnot and co-workers^{17, 18} (1933), on the contrary, observed quite the opposite effects. They produced ulcer by injecting varying amounts and concentrations of hydrochloric acid directly into the stomach wall. They then attempted to observe any effect of the addition of 1 mg. histamine.

They found that the ulcers were not located exclusively along the lesser curvature and were more numerous. The lesions presented a hemorrhagic appearance and some ulcers appeared more chronic with less tendency to heal.

Flood and Howes³⁸ (1934) observed that the subcutaneous administration of histamine interfered with the healing of a mucosal defect in the prepyloric region of the stomach of the cat and dog, but had little effect if the defect were made high on the greater curvature.

Orndorff, Bergh, and Ivy⁵⁸ (1935) made a very diligent effort to produce ulcer with histamine. They injected dogs with 2 mg. of aqueous histamine every two hours, ten times a day. During the remaining four hours, the animals were fed. They produced erosions in the duodenum of four of nine dogs but no true ulcers. Using pilocarpine in 2.5 mg. doses, they observed extensive mucosal hemorrhages throughout the stomach and intestine in six of thirteen dogs. Employing a combination of histamine and pilocarpine, they observed mucosal hemorrhages and erosions in thirteen of twenty-five dogs, but no instance of a definite ulcer.

Heinlein and Kastrop⁴⁸ (1938), using cats, noted a gastritis with edema and mucosal hemorrhages following large intravenous doses of histamine but failed to observe either erosions or ulcers. They noted an elevation of the acid values, but believed they played only a secondary role in the genesis of ulcer.

Code and Varco¹⁹ (1940) first noted the profound sustained effect upon gastric secretion following the injection of a histamine-beeswax mixture. Copious quantities of highly acid juice were secreted and the effect lasted at least twenty-four hours in the majority of cases.

Walpole and co-workers¹¹⁰ had been able to produce erosions and ulcerations in cats quite readily by the daily instillation of 0.4 per cent hydrochloric acid. They, therefore, attempted a comparison between ulcer production in response to endogenous and exogenous acid. Seven cats were injected with daily doses of 20 mg. of histamine, and ulcers were noted in all instances.

Varco¹⁰⁸ utilized the same technique but used the dogs with significant results. Typical gastric and duodenal ulcer occurred in every instance. It thus became apparent that the duodenal ulcers were due

to the continuous excessive secretion of a highly acid gastric juice, evoked by the histamine-beeswax mixture.

Hay and associates⁴⁷ (1942) extended the study to include nearly all the common laboratory animals as well as the pig, chicken, calf, and woodchuck.

Typical gastric and duodenal ulcers were again observed in a high percentage of animals studied, indicating the applicability and merit of the method. By substituting caffeine rather than histamine in the beeswax mixture, Judd⁵⁵ was able to produce ulcerations in cats and guinea pigs and, similarly, using morphine. Merendino⁸⁰ produced ulcer also in cats and guinea pigs.

Thus, for the first time, a method became available for producing typical chronic gastric and duodenal ulcers in a variety of intact laboratory animals. The importance of highly acid gastric juice in the genesis of ulcer was definitely established.

G. Miscellaneous Methods.—Bolton¹³ (1910) produced acute gastric ulcer in the cat by utilizing a "gastrotoxin" prepared by immunizing a goat with a cat's gastric cells. He then injected the goat's serum into the stomach wall of the cat, producing an acute ulcer.

Mann⁷² (1916) noted acute ulcers in a large percentage of dogs and cats dying after bilateral adrenalectomy where symptoms of adrenal insufficiency had developed.

Ivy⁵² noted four acute ulcers and numerous petechial hemorrhages in twenty-four thyroid-parathyroidectomized dogs.

Shapiro and Ivy⁹⁹ (1926) produced acute ulcers with local allergic phenomena by sensitizing an animal to a specific protein.

Wolfer¹²⁰ (1926) exposed the lumen of the stomach and gave x-ray radiation for thirty minutes with subsequent development of ulcer.

Kabat and Hedin⁵⁶ noted erosions and ulcerations in cats, following severe burns, and Merendino⁸⁰ has produced ulcer by fracturing the long bones of experimental animals, both methods probably being related to the release of histamine or a histamine-like substance.

Thus, in summary, after a fairly complete survey of the literature, it would appear that Code's method of the implantation of a histamine-beeswax mixture provides the best means of producing typical chronic duodenal and gastric ulcer. It is freely admitted that ulcer may be produced by a variety of methods, but the majority of them invoke alteration of the normal anatomy and physiology of the animal.

The value of producing typical lesions at will, in an intact animal, is obvious and Code's methods fulfill that criterion admirably.

DESCRIPTION OF THE METHOD, OPERATIVE PROCEDURES AND RESULTS

For nearly fifty years, surgeons have been treating ulcer quite empirically, employing a variety of operations without any definite knowledge of what their operation would accomplish. Their only criterion of success was the prevention of recurrence of the ulcer. It is indeed unfortunate that the initial improvement which follows almost any operative procedure upon the stomach was not better understood. Nearly any operation which increases the emptying time of the stomach and deviates the acid gastric juice away from the ulcerated duo-

denum will allow healing of the duodenal ulcer, only to be followed at some future date by the even more distressing jejunal ulcer.

Thus, surgeons, encouraged by their early successes and without appreciating the unfortunate results to come, performed operations in increasing numbers and eventually found many of their patients in a far worse predicament than if no operation had been done. One cannot help but wonder how many lives have been lost by inflicting upon patients such disastrous operations as those suggested by Von Eiselsberg,¹⁰⁰ Schmilinsky,⁹⁷ and Devine²⁷ when these people might have struggled along for years, suffering intermittently with their ulcers but still alive. It is not surprising that internists became hesitant to suggest operation to their patients when no definite improvement could be assured.

All this has changed. The importance of the acid factor has been demonstrated repeatedly and convincingly. Thus, the most important criterion which a satisfactory operation for ulcer must fulfill is effectual reduction of gastric acidity. Operations which fail to accomplish this leave too much to chance and will certainly be followed by a definite percentage of failure. With the means available for producing ulcer consistently in a number of laboratory animals, the protective influence of a variety of operative procedures may be assayed. The patient need no longer be made to serve as an experimental animal for new and untried procedures.

The value of twelve operative procedures has been subjected to experimental scrutiny and an attempt made to correlate the findings with the clinical data already available.

These operations include the majority of the commonly employed procedures in the surgical treatment of ulcer with the possible exception of pyloroplasty which was omitted because of its close relationship to gastrojejunostomy.

It is admitted that surgery is not the final answer to the ulcer problem. Surgical intervention is necessary only because medical management fails and the surgeon would be the first to relinquish his part if other equally as satisfactory conservative means were at hand. It is somewhat of an admission of defeat to remove an extensive segment of the stomach to heal a small stubborn duodenal ulcer and might be likened to the sacrifice of a lower limb in an attempt to control a diabetic gangrene involving only the toes and foot.

However, until better means are available, it would appear that surgery offers the best chance of effectively controlling gastric acidity.

The rarity of spontaneous ulcer in the dog has been recognized by a number of investigators,^{52, 72, 104} therefore, dogs were chosen as the laboratory animals for these investigations.⁶³

The dogs were fasted for twelve hours prior to operation. The operative procedures were done under intratracheal ether anesthesia. All anastomoses were accomplished by the closed aseptic technique as described by Wangenstein.¹¹¹ The animals were supported during the immediate postoperative period by daily intravenous infusion of glucose and saline solutions.

A period of three months was then allowed to elapse before the histamine injections were initiated to insure complete recovery from

the operative procedures. During this period, the animals were fed the usual stock diet consisting of commercial dog biscuit, supplemented occasionally by raw meat and table scraps.

The injection periods were then instituted. These were done daily, at about 5 P.M., following which the feed pans were removed and no food was allowed until the next morning. The technique of preparing the histamine-in-beeswax mixture has been described in detail elsewhere^{20, 47} and the daily dose of 30 mg. of histamine base was employed in all instances. The injections were made intramuscularly in multiple sites along the spinal muscles to insure adequate liberation of the histamine.

The symptoms of a developing ulcer were usually easily recognized. The animals became listless, cachectic, refused food, and, frequently, blood vomitus or tarry stools could be observed. Obviously moribund animals were sacrificed in order to obtain fresh autopsy specimens. The surviving animals were sacrificed at the end of the forty-day injection period. In each series of animals control dogs were injected and all of them developed typical duodenal ulcer. Grossly, these ulcers are quite similar in appearance to those developing spontaneously in man, with hemorrhage, excavation, induration, and perforation being commonly observed.

Microscopic sections of the ulcer were made in each instance and the findings were quite uniform. The free perforations obviously showed a loss of all the layers of the bowel wall and the chronic ulcers demonstrated a loss of the mucosal and submucosal layers with heaped-up overhanging edges and a leucocytic infiltration at the base of the ulcer. No tendency toward healing was noted.

I. Group I—Gastrojejunostomy

Gastrojejunostomy is perhaps the oldest of the operative procedures employed in the treatment of ulcer. Although Wölfler's initial procedure (1881) was for inoperable carcinoma, the operation of von Hacker (1885) was quite similar to the one usually done today.

About the turn of the century, reports of jejunal ulcer following gastrojejunostomy began to appear in the literature. Thus, surgeons began to seek out other more satisfactory procedures. The European surgeons were far in advance of the American surgeons in employing the more radical gastric resection in the treatment of ulcer.

Gastrojejunostomy continued to enjoy widespread popularity in this country with the exception of a few surgeons as A. A. Berg, Lewinohn, and Strauss, who pioneered the more radical gastric resection.

The formidable mortality which accompanied gastric resection in its early years makes it easily understandable why the less hazardous gastrojejunostomy was more acceptable.

However, with the present-day mortality rate of resection comparing favorably with that of gastrojejunostomy and the numerous unfavorable reports of jejunal ulcer following the conservative procedure, the once widespread popularity of gastrojejunostomy is waning. The incidence of ulcer, following gastrojejunostomy, ranging between

per cent, and is probably due to difference in indications and age groups. Instances of recurrent ulcer, developing from twenty to thirty years following the initial gastrojejunostomy, are not unusual although the average interval is probably about five years.

Thus, a true estimate of the ultimate occurrence must certainly approach 15 per cent.

The alleged benefits of gastrojejunostomy are due not only to the new avenue of escape for the stomach contents but also to the regurgitation of the alkaline duodenal juices into the stomach with neutralization of the gastric secretion.

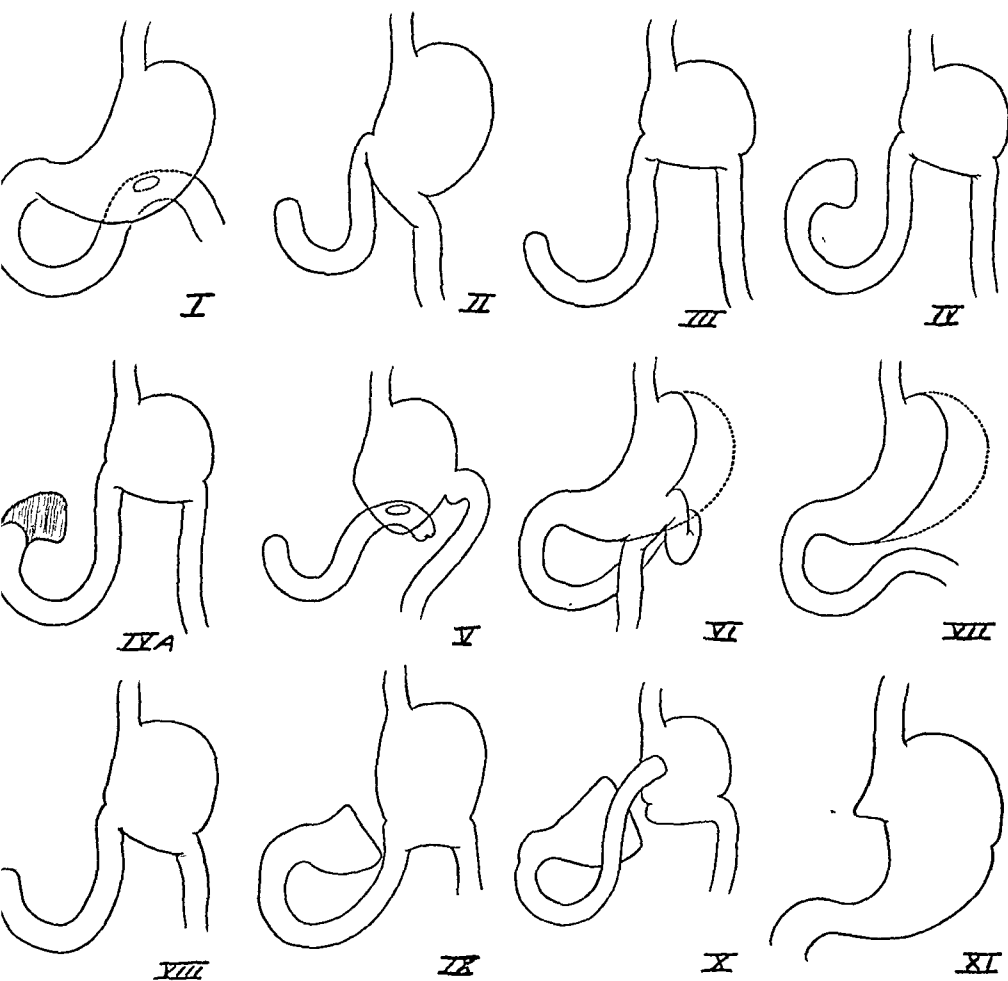


Fig. 1.—I, Gastrojejunostomy; II, small gastric resection or antral excision; III, extensive three-quarter gastric resection; IV, Finsterer antral exclusion; IVA, Finsterer antral exclusion with excision of antral mucosa; V, antral resection plus total intragastric regurgitation, *Schmilinsky* procedure; VI, fundusectomy with gastrojejunostomy; VII, hemigastrectomy; VIII, Devine exclusion; IX, modified Devine exclusion with total intragastric regurgitation; X, sleeve resection of segmental gastrectomy.

Although the gastric acidity is usually lowered following this procedure, in the experience of this clinic, none of the patients with duodenal ulcer studied was persistently achlorhydric and the incidence of jejunal ulcer was 10 per cent.^{114, 115} Therefore, the procedure has been almost entirely abandoned in this clinic, and only seven deliberate gastrojejunostomies for ulcer have been performed in the past five years.

TABLE I

INCIDENCE OF JEJUNAL ULCER FOLLOWING GASTROJEJUNOSTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
1	34	3	Perforated* 2.5 cm. jejunal ulcer	Dog expired, peritonitis
2	29	40	2 cm. jejunal ulcer	Also numerous erosions in jejunum
3	36	13	Perforated 1.5 cm. jejunal ulcer	Dog expired, peritonitis
4	30	40	2 cm. jejunal ulcer	

*See Fig. 2.

Gastrojejunostomy was performed on four dogs. It will be noted (Table I) that ulcer developed in all the animals, and two dogs expired from peritonitis, due to large, perforated jejunal ulcers.

It thus becomes apparent that this operation offers no protection against the development of ulcer but, on the contrary, appears to expedite its occurrence. All the ulcers developed in the jejunum, and no duodenal or gastric ulcers were observed.

It must be admitted that this operation occasionally is of value, especially in the older patients whose principal difficulty is obstruction, but with the operative risk of gastric resection approaching that of the more conservative gastrojejunostomy, these instances must be quite infrequent.

II. Group II—Small Gastric Resection or Antral Excision

It is the small gastric resection or antral excision which is partly responsible for the statement that gastric resection offers no more protection against the occurrence of recurrent ulcer than does gastrojejunostomy.

It is not unnatural that surgeons undergoing the transition between the conservative and the more radical procedures were somewhat timid in the extent of their resection. Thus, the first partial gastrectomies were hardly more than pylorectomies or antrectomies.

However, recurrent ulcers were also observed following this operation and thus gastric resection fell into disrepute.

The operation fails to reduce adequately gastric acidity and must be considered unsatisfactory. In a small series of cases observed in this clinic, none of the patients was persistently achlorhydric following this procedure and the incidence of jejunal ulcer was 33 per cent.¹¹⁴

TABLE II

INCIDENCE OF JEJUNAL ULCER FOLLOWING SMALL GASTRIC RESECTION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
185	35	40	2 cm. jejunal ulcer	
187	32	40	2 cm. jejunal ulcer	
196	35	35	2 cm. jejunal ulcer*	Ulcer almost perforated, also marked jejunitis
26	15	40	1 cm. jejunal ulcer	Dog moribund, entire intestinal tract filled with old blood

*See Fig. 3.

per cent, and is probably due to difference in indications and age groups. Instances of recurrent ulcer, developing from twenty to thirty years following the initial gastrojejunostomy, are not unusual although the average interval is probably about five years.

Thus, a true estimate of the ultimate occurrence must certainly approach 15 per cent.

The alleged benefits of gastrojejunostomy are due not only to the new avenue of escape for the stomach contents but also to the regurgitation of the alkaline duodenal juices into the stomach with neutralization of the gastric secretion.

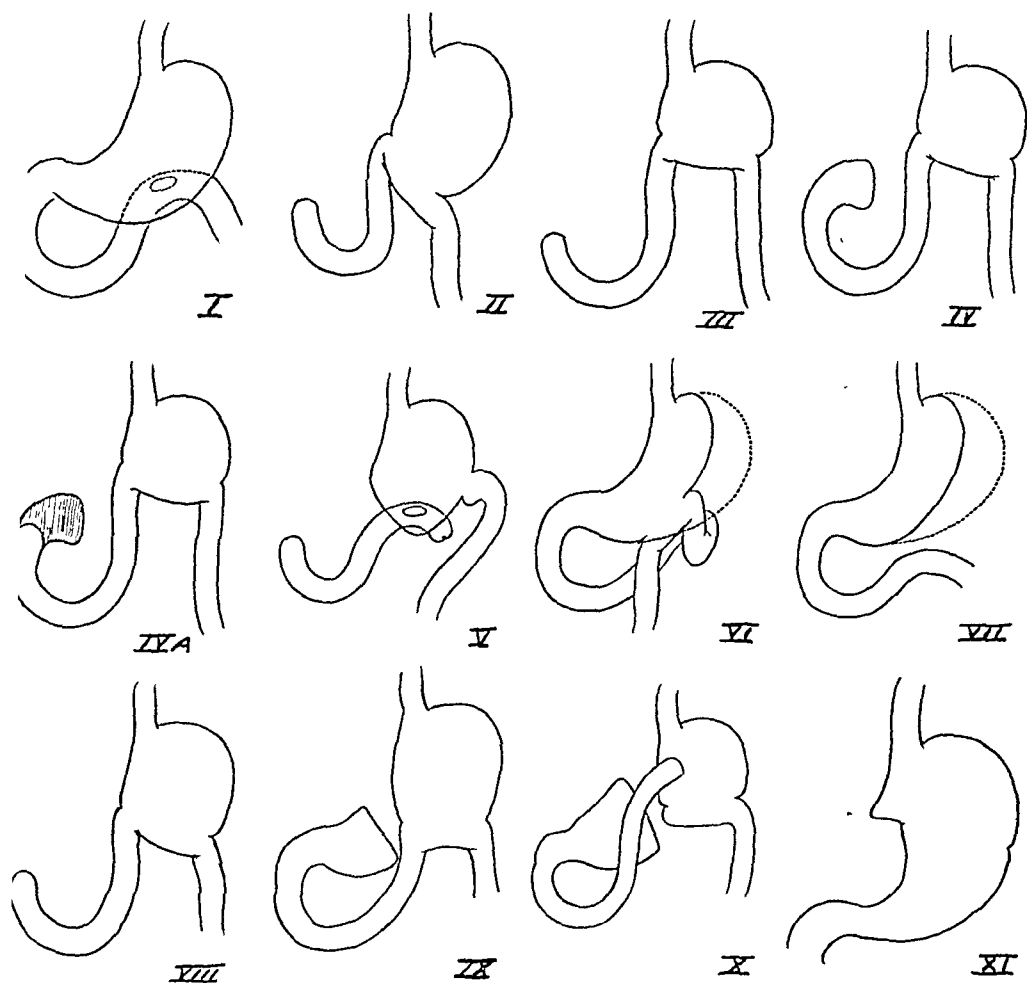


Fig. 1.—I, Gastrojejunostomy; II, small gastric resection or antral excision; III, extensive three-quarter gastric resection; IV, Finsterer antral exclusion; IVA, Finsterer antral exclusion with excision of antral mucosa; V, antral resection plus total intragastric regurgitation, Schmilinsky procedure; VI, fundusectomy with gastrojejunostomy; VII, fundusectomy; VIII, hemigastrectomy; IX, Devine exclusion; X, modified Devine exclusion with total intragastric regurgitation; XI, sleeve resection of segmental gastrectomy.

Although the gastric acidity is usually lowered following this procedure, in the experience of this clinic, none of the patients with duodenal ulcer studied was persistently achlorhydric and the incidence of jejunal ulcer was 10 per cent.^{114, 115} Therefore, the procedure has been almost entirely abandoned in this clinic, and only seven deliberate gastrojejunostomies for ulcer have been performed in the past five years.

some variation in different clinics. The surgeon must be able to show good reason for sacrificing an extensive segment of stomach.

The ideal resection should remove a portion of the stomach which will effectively control gastric acidity and insure protection against recurrent ulcer and yet leave the patient with a residual pouch large enough to provide a satisfactory gastric capacity. The three-quarter resection would appear to satisfy this requirement.

This operative procedure includes resection of the distal 75 per cent of the stomach, followed by anastomosis with the first portion of the jejunum and inversion of the lesser curvature, according to the Hofmeister pattern. This operation was done on four dogs.

TABLE III
INCIDENCE OF JEJUNAL ULCER FOLLOWING EXTENSIVE GASTRIC RESECTION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
6	38	40	No ulcer	
23	20	40	No ulcer	
24	47	40	No ulcer*	Few small submucosal hemorrhages in gastric pouch
28	27	40	No ulcer	Mild gastritis with 1 small erosion adjacent to esophagus

*See Fig. 4.

Thus, this operation completely protects the dog against the development of an experimentally induced ulcer. The resection of an extensive segment of the stomach alone, however, is not enough, as additional factors must be considered.

The importance of the length of the proximal afferent loop cannot be overemphasized. The increasing susceptibility to acid gastric juice of the lower intestinal tract has been attributed to decreased tissue resistance by Harper,^{45, 46} McMaster,⁷¹ Matthews and Dragstedt,⁷⁹ and others. Although there is good evidence to support this thesis, it seems possible that another factor may play a role. It has been shown that the duodenum and the upper jejunum are the most potent sources of "secretin," the hormone which regulates the secretion of the alkaline pancreatic juice.⁴ It is also known that the acid gastric secretion is necessary to activate the secretin and this stimulates the secretion of pancreatic juice. Thus, if the acid gastric secretion were introduced into the jejunum, below the secretin-containing segment of duodenum and upper jejunum, the secretion of pancreatic juice might be inadequate to neutralize the acid gastric juice, and jejunal ulcer would result. Studies are now being made to determine which of the two factors, tissue susceptibility or the secretin response, is the more important. However, no matter which mechanism is the more responsible, sufficient experimental and clinical evidence is available to condemn the long afferent loop. Merendino⁸⁰ has performed extensive three-quarter gastric resection in the dog and, by employing a long 75 cm. afferent loop, has observed two perforated jejunal ulcers after employing the histamine-in-beeswax injections.

Kiefer,⁵⁹ reporting the experiences of the Lahey Clinic, admits an incidence of recurrent ulcer in 12 (6.9 per cent) of 173 patients upon

whom an extensive gastric resection had been performed for duodenal ulcer. An additional 8 patients (4.6 per cent) exhibited postoperative hemorrhage although no definite ulcer was demonstrated. Thus, the results obtained in 20 (11.5 per cent) patients were clearly unsatisfactory. The gastric resection was apparently quite extensive but Lahey is an ardent advocate of the long loop anterior anastomosis.

In a recent review from this clinic, the results following 241 resections were studied.⁶² Of that number, 140 operations were done for duodenal ulcer, 23 for duodenal and gastric ulcer occurring coincidentally, and 25 for gastrojejunal ulcer. The remainder of the operations were done for gastric and pyloric ulcers.

The operation done in every case was the three-quarter resection with the anastomosis being made posterior to, right at, or even proximal to, the ligament of Treitz. Not a single instance of recurrent jejunal ulcer has been observed following this procedure.

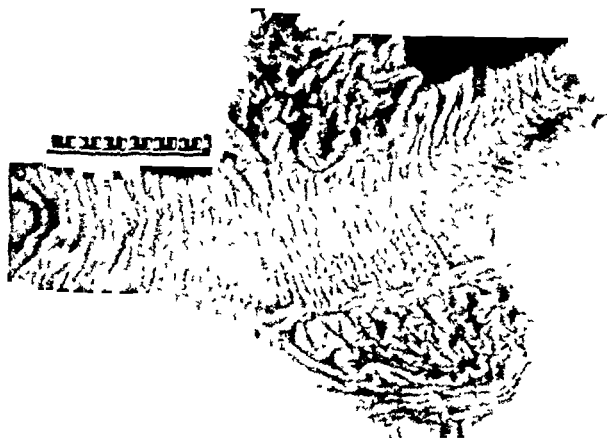


Fig. 4.—Normal jejunum (Dog 24) after extensive gastric resection. Note the short afferent loop. Dog sacrificed after forty injections of histamine-in-beeswax mixture.

Thus, experimental and clinical evidence clearly favors the short afferent loop. It is unfortunate that technical difficulties render impossible the employment of the Billroth I pattern of anastomosis as it would certainly be the most physiologic procedure.

The extensive three-quarter resection with the short loop anastomosis would thus appear to be most satisfactory, both from an experimental and clinical background.

It might indeed be argued that a slightly less extensive resection would prove equally as satisfactory, especially in the cases in the older age group or in the patients with gastric ulcer.

However, the results following approximately 300 resections, which have been done to date for gastric and duodenal ulcer, have been so consistently gratifying, that it would not seem necessary to employ a less certain procedure.

IVA. Finsterer Antral Exclusion With Excision of Antral Mucosa

This operative procedure is identical with the Group III operation except for the technical variation of inversion of the duodenum. The difficulties in dealing with the so-called "inoperable" duodenal ulcer are familiar to all gastric surgeons. They are also aware of the unhappy results obtained when attempting to deal with such a problem by employing one of the exclusion procedures of Von Eiselsberg,¹⁰⁹ Finsterer,³⁷ or Devine.²⁷

Although actual excision of the ulcer is unimportant, the necessity of ablating the antral mucosa is now quite apparent. A number of surgeons, notably, Plenk,⁹³ Bancroft,² Wolfson and Rothenberg,¹²¹ and Wangenstein^{112, 113} have concerned themselves with this problem. The "gastrin" thesis of Edkins has previously been mentioned.

Thus, the antral mucosa is excised and the closure accomplished by employing the antral musculature. This procedure was done on four dogs (see Table IVA).

TABLE IVA

INCIDENCE OF JEJUNAL ULCER FOLLOWING FINSTERER ANTRAL EXCLUSION
WITH EXCISION OF ANTRAL MUCOSA

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
46	26	40	No ulcer	Several erosions in gastric pouch, especially about esophagus; antral musculature markedly shrunken
48	35	40	No ulcer	Findings similar to Dog 13
64	48	40	No ulcer	
82	36	40	No ulcer	

The results (Table IVA) in this group are thus equally as acceptable as those in the previous series.

Although this procedure is of little experimental value, it has proved to be an invaluable adjunct in dealing with what might be an exceedingly difficult situation. This procedure has now been done in approximately forty patients with equally as satisfactory results as following the Group III operation.

IV. Finsterer Antral Exclusion

This procedure is again identical with the Group III operation except for the antrum which is not removed. The stomach is divided about 5 to 6 cm. proximal to the pylorus and the distal end is inverted. The operation was done on four dogs.

In attempting to correlate the findings in this group (Table IV) with the Edkins' hypothesis, it would appear that the results are suggestive but not conclusive. The erosions in the gastric pouch were more numerous than in either of the two preceding groups but the findings in the jejunum were essentially unchanged.

Fauley, Strauss, and Ivy³⁶ did Finsterer type resections in twelve dogs and observed the development of three (25 per cent) jejunal ulcers within seven months. They excised about 66 per cent of the stomach, including the antrum, and made the anastomosis with the first loop of jejunum.

TABLE IV

INCIDENCE OF JEJUNAL ULCER FOLLOWING FINSTERER ANTRAL EXCLUSION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF INJECTIONS	RESULTS	REMARKS
12	43	32	Several erosions in jejunum with marked jejunitis	Dog expired after 3 injections
29	41	40	No ulcer	Numerous erosions throughout gastric pouch with antral gastritis
30	37	40	No ulcer	Numerous erosions in gastric pouch
36	37	40	No ulcer	As in Dog 19

In this clinic, the incidence of jejunal ulcer following this type of operation is 8.5 per cent and other surgeons have reported even more unsatisfactory results. One patient, in particular, illustrates the significance of the antrum quite convincingly. Following a Finsterer exclusion operation, he continued to have difficulty and exhibited high acid values repeatedly. At a secondary operation, the residual antral segment, which measured only 16 sq. cm., was excised, following which the patient became almost completely achlorhydric with a complete cessation of symptoms.

Thus, although conclusive experimental data are lacking, accumulated evidence would suggest that this procedure should be discarded in favor of the Group III or IVA operation.

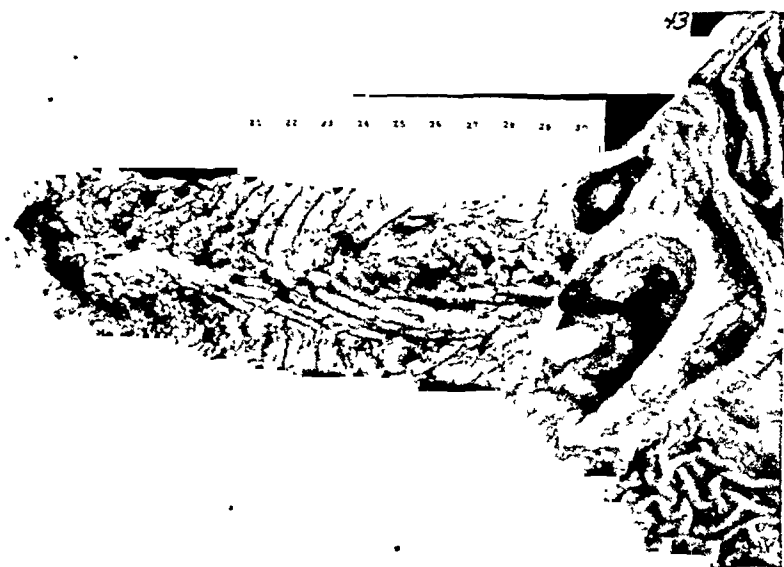


Fig. 5.—Multiple jejunal ulcers (Dog 43) following Schmilinsky procedure. Dog expired from hemorrhage and peritonitis after eleven injections of histamine-in-beeswax mixture.

V. Antral Resection Plus Total Intragastric Regurgitation

This procedure as advocated by Schmilinsky⁹⁷ was performed on four dogs.

The entrance of all the alkaline bile and pancreatic juice into the stomach would at first sight appear to be a desirable feature. However, it soon became apparent that it was quite the contrary.

TABLE V
INCIDENCE OF JEJUNAL ULCER FOLLOWING ANTRAL RESECTION PLUS
TOTAL INTRAGASTRIC REGURGITATION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
38	27	40	1.5 cm. jejunal ulcer	
41	27	2	Perforated 1 cm. jejunal ulcer	Dog died, peritonitis
43	40	11	4 jejunal ulcers, * 2 perforated	Dog died, peritonitis; also old blood in intestine
49	47	8	Perforated 1 cm. jejunal ulcer	Dog died, peritonitis

*See Fig. 5.

The explanation of such a formidable incidence of jejunal ulcer is not altogether clear, although it might be due to an interminable stimulation of the second (gastric) phase of gastric secretion by the bile and pancreatic juice or a failure of liberation of secretin.

Whatever the explanation, it is obvious that this procedure enhances, rather than protects against, the development of jejunal ulcer and is thus to be condemned. Fortunately, it was only performed on three patients, two (66 per cent) of whom promptly developed jejunal ulcer.¹¹⁴

VI. Fundusectomy With Gastrojejunostomy

This procedure was first suggested by Connell in 1929.²² He maintained that excision of the fundic portion of the stomach would effectively reduce gastric acidity and recommended the operation for its simplicity because no anastomosis was necessary.

However, Seely and Zollinger⁹⁸ and Watson¹¹⁶ have shown that although acid values may be initially reduced, within a few months they will return to preoperative levels.

In this group, fundusectomy was combined with gastrojejunostomy and was done on four dogs.

TABLE VI
INCIDENCE OF ULCER FOLLOWING FUNDUSECTOMY WITH GASTROJEJUNOSTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
31	42	40	No ulcer	Mild jejunitis
33	35	40	No ulcer	Few erosions in gastric pouch
54	40	40	No ulcer	
78	30	40	No ulcer	

Thus, this procedure appears to furnish satisfactory protection against the development of jejunal ulcer (Table VI) although, clinically, the gastric capacity following this operation is less adequate than that following the Group III or IVA procedure as the most dilatable portion of the stomach is removed. No jejunal ulcer has been observed clinically in eight patients upon whom this operation has been done, although only two (25 per cent) are persistently achlorhydric.

VII. Fundusectomy

The operation in this series approximates Connell's original description and was done on four dogs.

TABLE VII
INCIDENCE OF ULCER FOLLOWING FUNDUSECTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
19	32	40	No ulcer	Mild antral gastritis
21	25	40	Small duodenal erosions	Marked antral gastritis
22	37	40	Duodenal erosion	Antral gastritis
75	27	40	Duodenal* ulceration	Submucosal antral hemorrhages

*See Fig. 6.

This procedure, therefore, offers less protection than the preceding one (Table VII). Both again offer opportunity to evaluate Edkins' hypothesis. It would appear, especially from the results in Group VII, that the evidence favored the Edkins' thesis as although the extent of the resection in this group (VII) is as great as in the Group III or IVA operation, the findings following fundusectomy, in which the antrum remains in situ, are considerably different.

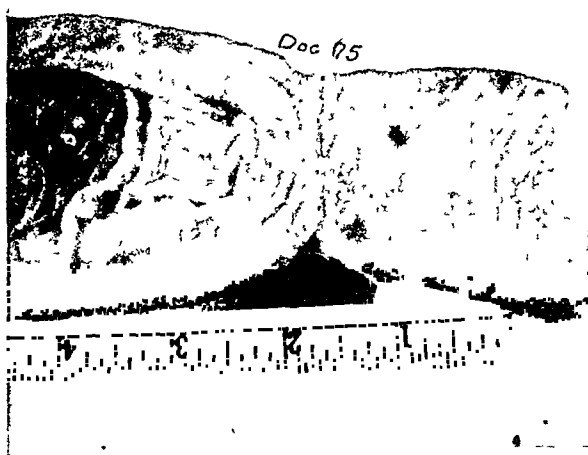


Fig. 6.—Duodenal ulcer (Dog 75) following fundusectomy. Dog sacrificed after forty injections of histamine-in-beeswax mixture.

None of the five patients upon whom this operation was done became achlorhydric and symptoms from the ulcer continue in two of them, one of whom subsequently had the antrum and pylorus excised.

Thus, the principle of fundusectomy cannot compete favorably with the Group III or IVA procedures, and the clinical indications for such an operation would also be much more limited.

VIII. Hemigastrectomy

Hunt⁵¹ has questioned the necessity of the extensive three-quarter gastric resection and advocated a more conservative procedure or hemigastrectomy. Accordingly, this operation was done on four dogs.

It would thus appear (Table VIII) that the operation does not furnish adequate protection. Hunt admits the possibility of an occasional jejunal ulcer but considers that less important than the impairment of gastric function which he alleges follows the more extensive resection.

TABLE VIII
INCIDENCE OF JEJUNAL ULCER FOLLOWING HEMIGASTRECTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
58	36	4	4 jejunal* ulcers, 1 per- forated	Dog died, peritonitis
62	31	40	No ulcer	Marked gastritis
73	18	40	No ulcer	
77	26	40	Jejunal erosion, no ulcer	

*See Fig. 7.

The experience of this clinic, however, would suggest that the weight of evidence tips the scales in the opposite direction. The unsatisfactory results and the necessity of even an occasional reoperation would appear to be far more disturbing than the incidence of any degree of impairment of gastric function observed in this clinic.



Fig. 7.

Fig. 7.—Multiple jejunal ulcers (Dog 58) following hemigastrectomy. Dog expired from peritonitis after four injections of histamine-in-beeswax mixture.



Fig. 8.

Fig. 8.—Large jejunal ulcer following Devine exclusion. Dog sacrificed after forty injections of histamine-in-beeswax mixture.

Hemigastrectomy would undoubtedly prove to be eminently satisfactory in a great majority of instances, but in the light of the gratifying results accompanying the Group III and IVA operations, it would not appear advisable to accept even a small incidence of recurrent ulcer.

IX. Devine Exclusion

No additional experimental evidence is necessary to bring to light the dismal record of this operation. The experience of surgeons with this unfortunate procedure has been uniformly disastrous.

TABLE IX

INCIDENCE OF JEJUNAL ULCER FOLLOWING DEVINE EXCLUSION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
88	38	34	Multiple jejunal ulcers; one 2 cm. ulcer	Dog died; peritonitis
89	42	40	Large 3 by 5 cm.* indur- ated jejunal ulcer	

*See Fig. 8.

It was added merely to complete the series and further test the efficiency of the method. The stomach was divided at about its lower third, the distal end inverted, and the jejunum anastomosed to the proximal gastric segment. This procedure was done on two dogs.

No further comment is necessary to condemn this procedure (Table IX).

X. Modified Devine Exclusion With Total Intra-gastric Regurgitation

The effects of total intra-gastric regurgitation have been mentioned and the failure of liberation of secretin suggested as a possible explanation. Thus the stomach was divided at about its mid-portion to assure the entrance of a definite quantity of acid gastric juice into the proximal loop. This loop was then implanted high on the fundus and the jejunum anastomosed to the proximal gastric segment. This procedure was done on two dogs.

TABLE X

INCIDENCE OF JEJUNAL ULCER FOLLOWING MODIFIED DEVINE EXCLUSION WITH TOTAL INTRAGASTRIC REGURGITATION

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
153	36	4	3 jejunal ulcers, 2 per- forated	
154	30	28	2 jejunal ulcers 1 to 2 cm. in diameter	Dog sacrificed, moribund

Thus, this procedure is equally unsatisfactory (Table X). If any protective influence did arise from the activation of secretin, it would appear to have been overcome by the torrent of acid gastric juice. The principle of intra-gastric regurgitation would thus appear to be unsatisfactory.

XI. Sleeve Resection or Segmental Gastrectomy

The sleeve resection procedure has also been quite uniformly discarded by surgeons. The central 50 per cent of the stomach was resected, following which the antrum was anastomosed to the remaining proximal (25 per cent) gastric pouch. This procedure was done on two dogs.

Although the experimental evidence is not conclusive (Table XI), the clinical limitations of such an operative procedure are obvious.

Suspected malignancy in gastric ulcers, duodenal obstructions, or hemorrhage would preclude the employment of this operation.

TABLE XI

INCIDENCE OF ULCER FOLLOWING SLEEVE RESECTION OR SEGMENTAL GASTRECTOMY

DOG NUMBER	WEIGHT (LB.)	NUMBER OF IN- JECTIONS	RESULTS	REMARKS
142	36	40	No ulcer	Few submucosal antral hem- orrhage
156	32	40	Small duodenal erosion	

Here again, the Edkins' hypothesis may be tested and, although not conclusive, the incidence would appear not to support this thesis as the extent of resection approximates that of the hemigastrectomy, but the results are certainly no worse and might even be better. It would appear, however, to support the Billroth I pattern of resection.

SUMMARY AND CONCLUSIONS

The preponderance of evidence suggests that the most important single factor in the causation of ulcer is an excess of unneutralized gastric acid. Accordingly, a satisfactory operation must control this item adequately. Code's histamine-in-beeswax preparation has made it possible to produce ulcer consistently in a variety of intact laboratory animals. It is also possible, therefore, to assay the protective ability of a number of operative procedures against the formation of ulcer. The experimental data obtained by employing this method would appear to substantiate the clinical data already available indicating the efficiency of this experimental approach to the ulcer problem. It also provides a means of evaluating any new or untried procedures without submitting the patient to an "experimental" operation.

A number of requirements which a satisfactory operation must fulfill have become apparent. First, an effective reduction of gastric secretion must be accomplished which necessitates the sacrifice of an extensive segment of gastric tissue, including the antrum and the lesser curvature.

Second, the manner of duodenal inversion, with or without removal of the ulcer, is of no great consequence, but all the antral mucosa must be removed.

Although experimental evidence favoring the Edkins' hypothesis is not conclusive, clinical experience has indicated clearly the importance of the antral mucosa.

Finally, the anastomosis with the jejunum must be made in such a manner that the proximal afferent loop is as short as possible. The possibilities of the secretin factor and decreased tissue susceptibility have been mentioned and the evidence condemning the long loop is conclusive.

1. Thus, gastrojejunostomy, hemigastrectomy, and the small gastric resection are inadequate operations, as they fail to reduce gastric secretion effectively.

2. The exclusion type of operation is unsatisfactory as the antral hormonal influence is uncontrolled.

3. The principle of total intragastric regurgitation is to be condemned.

4. The limited indications for the segmental resection or fundusectomy are mentioned.

5. The most satisfactory operation would appear to be an extensive three-quarter gastric resection, including the antrum, or at least the

64. Layne, J. A., and Bergh, G. S.: The Effect of Ligation of Arteries of the Stomach Upon Acid Gastric Secretion and Upon the Endoscopic Appearance of the Gastric Mucosa in the Dog, *Surgery* 13: 136-144, 1943.
65. Light, R. O., Bishop, C. C., and Kendall, L. G.: The Production of Gastric Lesions in Rabbits by Injection of Small Amounts of Pilocarpine Into the Cerebrospinal Fluid, *J. Pharmacol. & Exper. Therap.* 45: 227-251, 1932.
66. Litthauer, M.: Recherches experimentales sur la pathogenie de l'ulcers rond stomacal, *J. de chir.* 2: 424, 1909.
67. Lium, R.: Peptic Ulcer and Diarrhea Following the Removal of the Prevertebral Ganglia in Dogs, *Surgery* 9: 538-553, 1941.
68. Loewy, G.: Experience sur la production d'ulceres duodenaux par derivation isolee de la bile, *Bull. et mèm. Soc. nat. de chir.* 56: 243-249, 1930.
69. McCann, J. C.: Experimental Peptic Ulcer, *Arch. Surg.* 19: 600-659, 1929.
70. McIlroy, P. T.: Experimental Production of Gastric Ulcer, *Proc. Soc. Exper. Biol. & Med.* 25: 268-269, 1927-1928.
71. McMaster, P. E.: Effects of Diverting the Gastric Contents to the Lower Intestinal Levels, *Arch. Surg.* 28: 825-836, 1934.
72. Mann, F. C.: A Study of the Gastric Ulcers Following Removal of the Adrenals, *J. Exper. Med.* 23: 203-210, 1916.
73. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcers, *J. A. M. A.* 99: 1576-1582, 1932.
74. Mann, F. C., and Bollman, J. L.: The Reaction of the Content of the Gastro-Intestinal Tract, *J. A. M. A.* 95: 1722-1724, 1930.
75. Mann, F. C., and Kawamura, K.: Duodenectomy, *Ann. Surg.* 75: 208-220, 1922.
76. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* 77: 404-422, 1923.
77. Matsuda, A.: Zur experimentellen erzeugung des Magengeschwüre durch histamin, *Klin. Wchnschr.* 10: 2265, 1931.
78. Matthews, W. B.: Production of Intestinal Ulcers by Active Gastric Juice, *Proc. Soc. Exper. Biol. & Med.* 28: 960-961, 1931.
79. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, *Surg., Gynec. & Obst.* 55: 265-286, 1932.
80. Merendino, K. A.: Unpublished data, 1943.
81. Metz, M. H.: A Gastric Lesion Produced by Posterior Pituitary Extract, *Texas State J. Med.* 34: 295-297, 1938.
82. Metz, M. H., and Lackey, R. W.: Treatment of Peptic Ulcer With Posterior Pituitary Extract—Preliminary Report, *Texas State J. Med.* 32: 589-590, 1937.
83. Morton, C. B.: Observations on Peptic Ulcer, *Ann. Surg.* 85: 207-238, 1927.
84. Morton, C. B.: Observations on Peptic Ulcer, *Ann. Surg.* 85: 879-885, 1927.
85. Neuman, F., Demoor, P., and Delovers, L.: Contribution à l'étude de la pathogenie des ulceres gastro-duodenaux, *Compt. rend. Soc. de biol.* 105: 887-893, 1931.
86. Oberling, O., and Kalto, A.: Ulceres aigus de l'estomac consecutifs à des lesions experimentales des noyaux gris centraux, *Compt. rend. Soc. de biol.* 102: 832-833, 1929.
87. Ochsner, A., Gage, M., and Hosoi, K.: The Relationship of Peptic Ulceration to Gastric Chemism, *Proc. Soc. Exper. Biol. & Med.* 31: 1260, 1934.
88. Orndorff, J. R., Bergh, G. S., and Ivy, A. C.: Peptic Ulcer and the Anxiety Complex, *Surg., Gynec. & Obst.* 61: 162-168, 1935.
89. O'Shaughnessy, L.: Etiology of Peptic Ulcer, *Lancet* 220: 177-181, 1931.
90. Owings, J. C., and Smith, I. H.: Experimental Production and Cure of Jejunal Ulcers, *Proc. Soc. Exper. Biol. & Med.* 29: 832-833, 1932.
91. Owings, J. C., and Smith, I. H.: Etiology of Duodenal Ulcers, *Proc. Soc. Exper. Biol. & Med.* 29: 833-835, 1932.
92. Panum: Quoted by Cohnheim.²¹
93. Plenk, A.: Zur Technik der Resektion zur Ausschaltung, *Zentralbl. f. Chir.* 63: 3019, 1936.
94. Reeves, T. B.: A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer, *Surg., Gynec. & Obst.* 30: 374-385, 1920.
95. Rosenow, E. C.: The Causation of Gastric and Duodenal Ulcer by Streptococci, *J. Infect. Dis.* 19: 333-384, 1916.
96. Schiffrin, M. J.: Production of Experimental Jejunal Ulcer, *Proc. Soc. Exper. Biol. & Med.* 45: 592-594, 1940.
97. Schmilinsky, H.: Die einleitung der gesamten Duodenalsäfte in den Magen (inner Apotheke), *Zentralbl. f. Chir.* 45: 416, 1918.
98. Seely, H., and Zollinger, R.: Fundusectomy in the Treatment of Peptic Ulcer, *Surg., Gynec. & Obst.* 61: 161-166, 1935.
99. Shapiro, P. F., and Ivy, A. C.: Gastric Ulcer—Experimental Production of Gastric Ulcer by Local Anaphylaxis, *Arch. Int. Med.* 38: 237-258, 1926.
100. Simonds, J. P.: Mode of Origin of Experimental Gastric Ulcer Induced by Cinchophen, *Arch. Path.* 26: 44-50, 1938.
101. Smith, D. T., and McConkey, M.: Peptic Ulcers (Gastric, Pyloric and Duodenal), *Arch. Int. Med.* 51: 413-426, 1933.

102. Stalker, L. K., Bollman, J. L., and Mann, F. C.: Experimental Peptic Ulcer Produced by Cinchophen, *Proc. Staff Meet., Mayo Clin.* 11: 695-698, 1936.
103. Turck, F. B.: Ulcer of the Stomach; Pathogenesis and Pathology, *J. A. M. A.* 46: 1753-1763, 1906.
104. Turck, F. B.: Quoted by Ivy.⁵²
105. Underhill, F. P., and Freiheit, J. M.: Effect of Pilocarpine and Epinephrine in the Production of Specific Lesions in the Stomach of Rabbits, *Arch. Path.* 5: 411-428, 1928.
106. Van Wagoner, F. H., and Churchill, T. P.: Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning, *J. A. M. A.* 99: 1859-60, 1932.
107. Varco, R. L.: Unpublished data, 1940.
108. Varco, R. L., Code, C. D., Walpole, S. H., and Wangensteen, O. H.: Duodenal Ulcer Formation in the Dog by Intramuscular Injections of a Histamine-beeswax Mixture, *Am. J. Physiol.* 133: 475-476, 1941.
109. Von Eiselsberg: Ueber Ausschaltung inoperabler Pylorusstrukturen nebst Bemaerkungen über die jejunostomie, *Arch. f. klin. Chir.* 50: 919-939, 1895.
110. Walpole, S. H., Varco, R. L., Code, C. F., and Wangensteen, O. H.: Production of Gastric and Duodenal Ulcers in the Cat by Intramuscular Implantation of Histamine, *Proc. Soc. Exper. Biol. & Med.* 44: 619-621, 1940.
111. Wangensteen, O. H.: Aseptic Gastric Resections: I. A Method of Aseptic Anastomosis Adaptable to Any Segment of the Alimentary Canal (Esophagus, Stomach, Small or Large Intestine); II. Including Preliminary Description of Subtotal Excision of the Acid-Secreting Area for Ulcer, *Surg., Gynec. & Obst.* 70: 59-72, 1940.
112. Wangensteen, O. H., Varco, R. L., Hay, L. J., Walpole, S. H., and Trach, B.: Gastric Acidity Before and After Operative Procedure With Special Reference to the Role of the Pylorus and Antrum: A Preliminary Report of a Clinical and Experimental Study, *Ann. Surg.* 112: 626-670, 1940.
113. Wangensteen, O. H.: Method of Closing the Pyloroantral Pouch in the Antral Exclusion Operation, *SURGERY* 12: 731-741, 1942.
114. Wangensteen, O. H., and Lannin, B. G.: Criteria of an Acceptable Operation for Ulcer and the Importance of the Acid Factor, *Arch. Surg.* 44: 489, 1942.
115. Wangensteen, O. H.: The Surgical Management of Ulcer: A Chemical Problem, *Proc. Interst. Postgrad. M. A. North America* Oct. 1942.
116. Watson, J. R.: Effect of Fundusectomy on the Acidity of the Gastric and Duodenal Content; An Experimental Study, *Arch. Surg.* 31: 1-9, 1935.
117. Weech, A. A., and Paige, B. H.: Nutritional Edema in the Dog, *Am. J. Path.* 13: 249-256, 1937.
118. Weiss, A. G., and Aron, E.: Role des amines dans l'évolution de l'ulcère experimental: Influence de l'histidine, *Presse méd.* 41: 1880, 1933.
119. Wilensky, A. O., and Geist, S. H.: Experimental Studies in the Production of Chronic Gastric Ulcer, *J. A. M. A.* 66: 1382, 1916.
120. Wolfer, J. A.: Chronic Ulcer of the Stomach: Its Experimental Production and Effect on Gastric Secretion and Motility, *Ann. Surg.* 84: 89-94, 1926.
121. Wolfson, W. L., and Rothenberg, R. E.: The Surgical Treatment of Complicated Duodenal Ulcer, *SURGERY* 3: 663-669, 1938.
122. Wu, P. P. T.: Reactions of Contents of Jejunum and Experimental Production of Peptic Ulcer, *Arch. Surg.* 30: 557-562, 1935.
123. Wu, P. P. T.: The Effect of Histidine on the Experimental Production of Peptic Ulcer, *Ann. Surg.* 106: 196-199, 1937.

REMOVAL OF THE VAGUS INNERVATION OF THE STOMACH IN GASTRODUODENAL ULCER

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THE capacity of pure gastric juice to digest living tissue has been demonstrated by numerous experimental studies. Although more resistant than other parts of the gastrointestinal tract, the mucous membrane of the stomach itself succumbs to the corrosive and digestant action of the fundus secretion under conditions where this secretion is not diluted or neutralized by pyloric mucus, duodenal secretions, or food.¹ It thus appears clear that under normal conditions the wall of the stomach escapes digestion because it is not exposed to the pure fundus secretion for long periods of time and not because of a special resistance to that secretion. The dilution and neutralization of the gastric juice by ingested food and drink during the periods of psychic and chemical stimulation of secretion are probably the chief factors that protect the gastric and duodenal mucosa. The importance of the continuous autoneutralization of the acid gastric juice by the duodenal secretions and the pyloric mucus has, however, been firmly established by numerous experiments. When the mixture of these secretions is prevented, progressive ulceration of the duodenum or stomach almost inevitably occurs. Thus, penetrating ulcers in the jejunum develop when the duodenal secretions are diverted into the ileum.² Ulcers in the jejunum, ileum, or colon occur when the gastric juice from a Pavlov or Heidenhain pouch is diverted into these areas of the intestine.³ Ulcers in the duodenum develop when the pancreatic juice is led to the outside by means of a total fistula.^{3, 4} These studies have focused attention on the necessity for more or less continuous neutralization of the fundus secretion, but so far a defect in this neutralizing mechanism has not been established as a causative factor in any large number of ulcers in man. The disease occurs chiefly in young adults without evidence of biliary or pancreatic disease or reason to suppose that these secretions are deficient.

An excessive secretion of gastric juice in the presence of normal amounts of the alkaline duodenal secretions might on theoretical grounds be expected to produce a situation similar to that resulting from deficient or absent duodenal secretions coupled with a normal gastric output. The gastric juice would finally overcome the neutralizing capacity of food and duodenal secretions and cause the appearance in the stomach and duodenum of a content approaching the pure fundus secretion in acidity and pepsin content. Evidence that such excessive gastric secretion experimentally produced in normal animals causes the appearance of typical ulcers has been provided by Wangensteen and his associates.⁵ Hypersecretion was secured by implanting pellets of a mixture of histamine and beeswax into the muscles and subcu-

Work aided by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

Received for publication, Oct. 16, 1944.

taneous tissues of dogs, cats, guinea pigs, and other animals and when this was continued, progressive perforating ulcers in the stomach and duodenum appeared.

That an excessive secretion of gastric juice occurs in most ulcer patients may be regarded as definitely established. Most of the data supporting this conclusion have been obtained by testing the response of the gastric glands to various types of stimulation. For the most part the stimuli employed have been chemical in nature, as for instance the Ewald test breakfast, alcohol installation, or the injection of histamine. On the whole these tests have demonstrated that ulcer patients secrete somewhat more gastric juice in response to these stimuli than do normal persons. The amount, however, is not sufficiently great or uniform to have much diagnostic value.⁶ Presumably, these chemical stimuli act directly on the parietal and chief cells of the gastric glands and any increased response obtained must be due to an increased excitability or sensitivity of these cells. Unfortunately, there has been little effort to test the secretory response of the stomach in ulcer patients to psychic stimuli and to compare this response with that of normal individuals. Such information would probably be of the greatest value. A sham meal consisting of appetizing food, that is, meat, vegetables, and fruit, could be thoroughly masticated but not swallowed. If this were done while constant suction was being made on a Levin tube introduced through the nose into the stomach, the gastric juice elicited could be obtained for measurement and titration. The caffeine test meal proposed by Roth, Ivy, and Atkinson,⁷ which apparently demonstrates a greater secretory response in ulcer patients as compared with normal people, probably also tests this neuroglandular mechanism. Evidence that the continuous night secretion of gastric juice in ulcer patients is greater than in normal individuals has been obtained in this clinic and has been presented elsewhere.⁸

Acting on the conception that the hypersecretion of gastric juice in gastroduodenal ulcer is very largely neurogenic in origin, a series of patients with this disease have been treated by an operation designed to remove permanently and as completely as possible the vagus innervation of the stomach. The first operations were performed in January and February, 1943, and were reported in June of that year.⁹ A further report of eleven patients was made before the meeting of the American Gastroenterological Association in Chicago, June 12, 1944.⁸ Since that report an additional four patients have been operated upon by the same method. It is the purpose of the present paper to discuss the operative procedure and to review the results to date.

An extensive experience with various procedures for studying gastric physiology in experimental animals suggested that the best method to secure complete division of the vagus nerves to the stomach would be to isolate these fibers in the chest before they pass through the diaphragm and enter the wall of the stomach. The desirability of such a complete operation was indicated by the studies of Hartzell.¹⁰ This investigator found that complete division of the vagus nerves in the thorax produced a marked and long-continued decrease in the free and total acidity of the gastric content secured in response to the ingestion of a test meal of lean meat. An incomplete division had

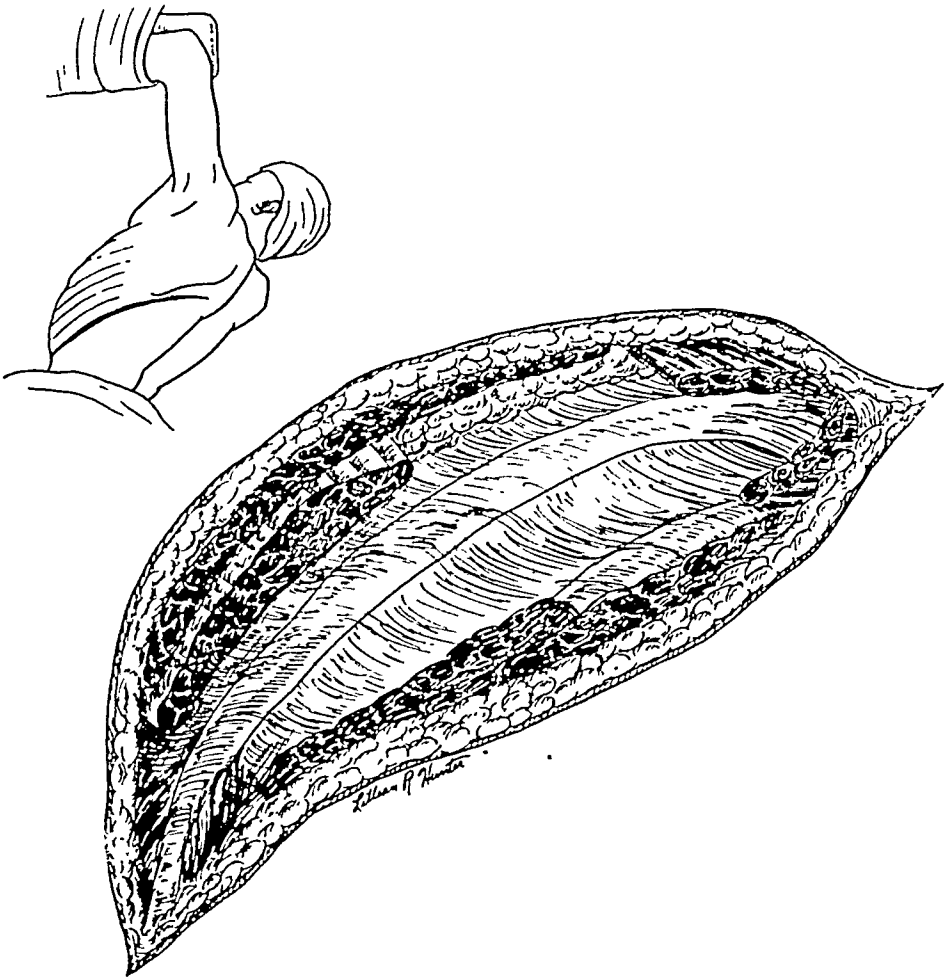


Fig. 1.

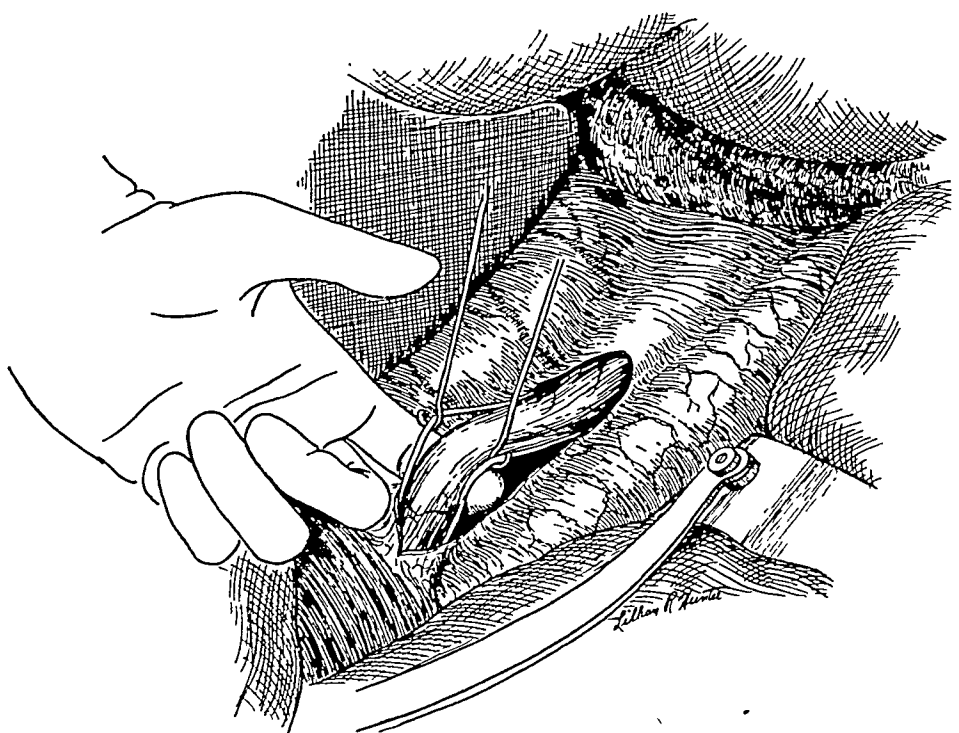


Fig. 2.

little or no effect. Data confirming and extending these observations have been secured in our laboratory by means of animals with totally isolated stomachs both with and without vagal innervation and will be reported elsewhere. The dog tolerates division of the vagus nerves low in the chest fairly well, although occasional animals vomit repeatedly and appear to have some difficulty in swallowing. The ab-

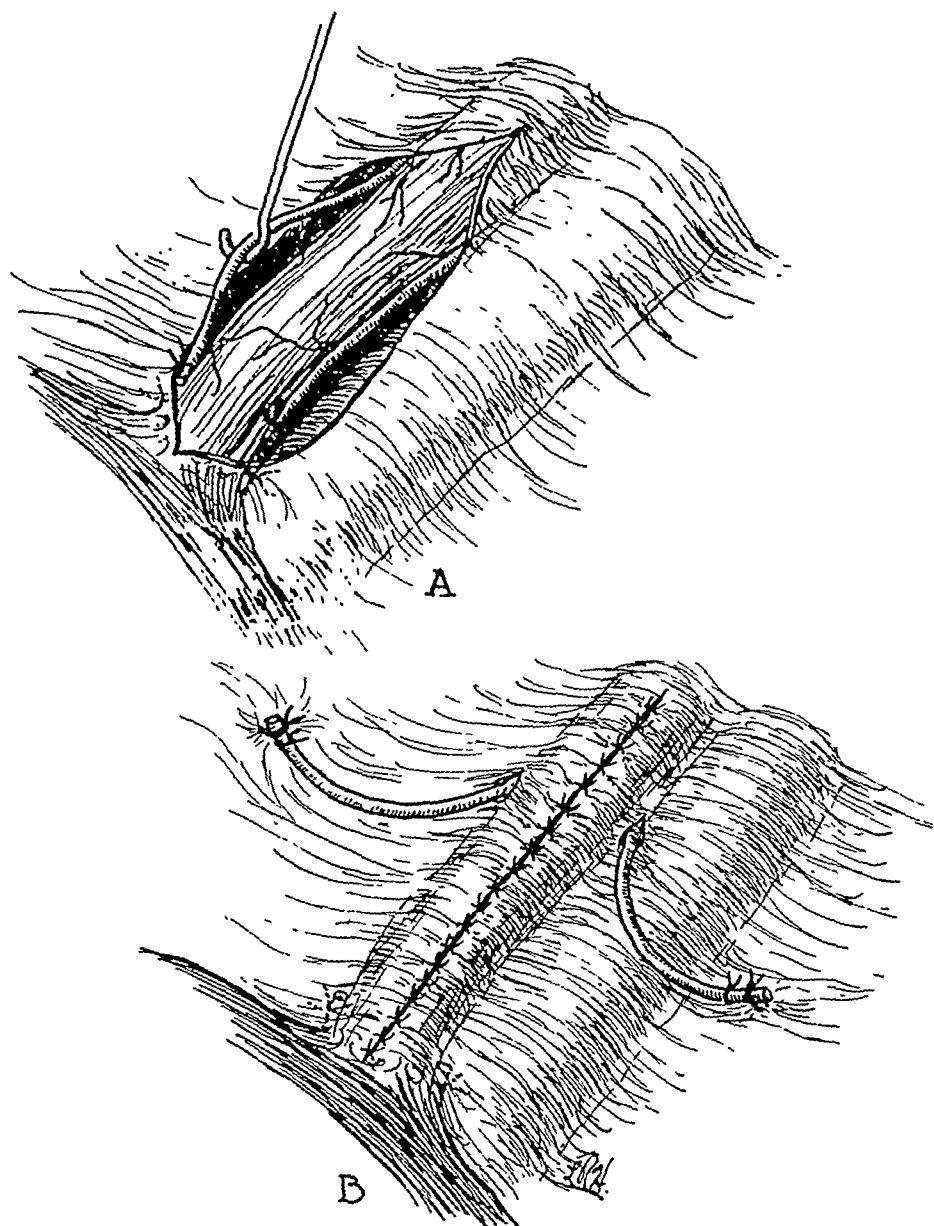


FIG. 3.

sence of adverse effects in man after excision of the lower esophagus for carcinoma, an operation which necessarily includes excision of the vagus nerves, prompted us to perform supradiaphragmatic section of the vagus nerves for the treatment of gastroduodenal ulcer.

The patients were anesthetized with ethylene and ether, using a positive pressure mask technique. An extensive resection of the seventh or eighth rib on the left side was then made (Fig. 1). In the

TABULATED SUMMARY OF DATA ON PATIENTS ON WHOM SUPRADIAPHRAGMATIC

PATIENT	AGE AND SEX	DURATION OF SYMPTOMS (YR.)	DIAGNOSIS	DIRECT VISUALIZATION OF ULCER WITH GASTROSCOPE	X-RAY EVIDENCE OF ULCER CRATER	PYLORIC STENOSIS	HEMORRHIAGE	PERFORATION	VOL. PREOP. NIGHT SECRETION
W. B.	51 ♂	13	Duodenal ulcer	+	+	++	+	+	1,160
J. J. F.	40 ♂	18	Duodenal ulcer	-	+	++	++	-	1,450
M. V.	34 ♀	17	Duodenal ulcer	-	-	+	-	-	1,000
J. J.	44 ♂	13	Duodenal ulcer	-	+	+++	-	-	780
J. A.	45 ♂	5	Gastric ulcer	+	+	-	+	-	840
S. S.	54 ♂	25	Duodenal ulcer	-	+	+	++	-	1,715
C. S.	38 ♂	2	Duodenal ulcer	-	-	+	-	-	971
V. M.	31 ♂	6	Duodenal ulcer	-	+	+	-	-	1,120
J. L.	46 ♂	29	Duodenal ulcer	-	+	+	++	-	800
A. J.	47 ♂	4	Duodenal ulcer	-	+	-	-	-	1,085
E. N.	17 ♂	6	Duodenal ulcer	-	+	+	-	-	1,855
M. D.	34 ♂	12	Duodenal ulcer	+	+	+	-	-	
M. B.	47 ♂	6	Duodenal ulcer	-	+	++	+	+	1,020
I. C.	28 ♂	8	Gastrojejunal ulcer	-	+	-	+	-	
F. C.	40 ♂	6	Duodenal ulcer	+	+	+	+	-	510

earlier cases a smaller portion of rib was removed and the rib above and below fractured to facilitate exposure. A more extensive removal of rib and cartilage in later cases provided better exposure and less trauma. It is possible that a very long intercostal incision would suffice but has not been tried to date. The left lung is mobilized by dividing and ligating the inferior pulmonary ligament, retracted upward and held out of the field by a rounded broad-bladed retractor. The pleura over the lower 10 cm. of the esophagus is then opened and the lower esophagus mobilized and elevated into the field with the finger. The main trunks of the left or anterior vagus and the right or posterior vagus are easily secured. In Fig. 2, these are depicted as single nerve trunks. In most cases, however, a varying number of branches exist which can be grouped into two main bundles and ligated. In addition to the main trunks which lie alongside of the esophagus, smaller fibers of the vagi penetrate the esophageal wall. These may

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SECTION OF THE VAGUS NERVES WAS PERFORMED FOR GASTRODUODENAL ULCER

VOL. P.O. NIGHT SECRE- TION	PREOP. FREE ACIDITY	P.O. FREE ACIDITY	DATE OF VAGUS SECTION	REMARKS
310	65	58	1/18/43	Complete relief of symptoms with no recurrence to 10/12/44
510	70	56	2/22/43	Complete relief, gained 40lb in weight, no recurrence to 10/12/44
---	62	--	5/21/43	Complete relief of distress for 3 mo., then recurrence; diagnosis uncertain
250	51	11	6/15/43	Complete relief of pain but persistence of obstructive symptoms in 10/44
455	40	0	7/ 7/43	Complete relief; gastroscopy 3/27/44 showed ulcer to be healed, no recurrence 10/12/44
688	25	36	7/28/43	Complete relief with no recurrence to 10/12/44
126	69	25	11/ 3/43	Complete relief with no recurrence to 10/12/44
674	74	40	5/ 1/44	Complete relief with no recurrence to 8/44
448	48	22	5/ 1/44	Complete relief with no recurrence to 9/20/44
353	41	30	5/ 9/44	Slight relief, continued nausea and vomiting; gastroenterostomy 7/3/44, complete relief 9/20/44
425	41	21	5/24/44	Complete relief with no recurrence to 10/12/44
			6/23/44	Slight relief, continued epigastric pain and nausea; gastroenterostomy 8/2/44, complete relief to 9/2/44
215	81	42	6/26/44	Symptoms relieved for 8 wk., then acute dilatation of stomach after ingestion of large amount of food; gastroenterostomy 10/44
			6/30/44	Partial relief, frequent feeding, and alkalis required to 8/5/44
450	50	0	7/ 7/44	Fluoroscopy 8/14/44 showed disappearance of crater

be identified and combed off by elevating the esophagus with the finger. The nerve fibers then stand out as cords against the more elastic muscle tissue. All of the nerve fibers that can be detected by this combined inspection and palpation are grouped into two main bundles ligated, and divided just above the diaphragm. In the first two cases segments of vagus fibers 3 to 4 cm. in length were excised. In subsequent cases the nerves have been ligated, divided, and the proximal ends brought out and sutured to the pleura as indicated in Fig. 3. The esophagus is then replaced in its bed, careful hemostasis secured and the overlying pleura closed with a running catgut suture. The transplantation of the nerves into the pleural cavity is done in an attempt to prevent regeneration. The chest is then closed without drainage. In the first five cases, a Pezzer catheter drain was introduced between the ribs and left in place for several days, but this has now been abandoned. In the early cases complete bed rest was secured for the first six postoperative days. In later cases, however, the pa-

tients have been encouraged to get out of bed for a brief period twenty-four hours after the operation, for increasing lengths of time each succeeding day, and by the fourth or fifth day are fully ambulatory. We have the impression that this early rising has many advantages and decreases the incidence and liability of pulmonary and other complications.

The results of the operation to date have been summarized in Table I. Of the fifteen patients, fourteen were males and one female. Thirteen had duodenal ulcers, one a gastric ulcer, and one a gastrojejunal ulcer. Evidence of the disease was present from two to twenty-nine years and for the most part the series represented chronic refractory disease that had persisted or recurred in spite of prolonged medical management. Serious hemorrhage had occurred in four patients, perforation in two, and craters were demonstrated in thirteen. Most of these patients secreted large volumes of highly acid gastric juice at night and this was markedly reduced by the division of the vagus nerves. The most striking result of the operation was the immediate and persistent relief of the ulcer pain and distress secured in most of the patients. This occurred so soon after operation as to suggest interruption of the sensory fibers responsible for these sensations by the vagus section. This is, however, not the sole explanation. In the patient with a gastric ulcer visualized with the gastroscope before operation, a later examination showed the ulcer to be completely healed. In eight of the patients with duodenal ulcer and in which a crater was demonstrated with the x-rays, subsequent examination by the same method indicated that the crater had disappeared. Nine of the patients gained considerable weight after the operation and in three of these the gain exceeded thirty pounds. In three patients a gastrojejunostomy was performed at varying periods after the vagus section because of persistence of obstructive symptoms and x-ray evidence of delayed emptying of the stomach. One of these patients (M. B.) is particularly instructive. This patient had a duodenal ulcer with a demonstrated crater and marked pyloric stenosis. Section of the vagus nerves produced relief from ulcer distress and for eight weeks the patient was apparently in good condition without medication or dietary restriction. Then, following the ingestion of a large amount of watermelon, he developed an acute dilatation of the stomach. When examined several days later, the dilated stomach extended to the symphysis and yielded, on aspiration, 5 L. of dark brown fluid slightly acid in reaction. Constant suction gastric drainage was then employed and subsequently a gastroenterostomy was performed. It is possible that the removal of the vagal influence with its augmentor effect on gastric tonus and motility may have played a role in the acute dilatation of the stomach in this patient. In two of the other patients a varying amount of atony of the fundus of the stomach was observed at fluoroscopy for the first week or two following the operation. In no case were symptoms suggestive of cardiospasm observed and fluoroscopic examination failed to reveal abnormalities in the function of the esophagus. Aside from the temporary gastric atony mentioned, the stomach appeared normal with respect to peristalsis, position, and tonus. No abnormalities were observed in the intestines

by x-ray and neither constipation nor diarrhea appeared. The most troublesome complication of the operation was the severe and often persistent pain in the region of the thoracotomy wound. In several cases this lasted for two to three weeks. It was probably due to tearing of the fibers of the intercostal nerve by retraction of the ribs and possibly could have been prevented by dividing or excising a portion of this nerve.

SUMMARY

Supradiaphragmatic division of the vagus nerves has been performed in thirteen patients with duodenal ulcer, in one patient with gastric ulcer, and in one with a gastrojejunal ulcer. The patient with gastric ulcer has been apparently cured of his disease as judged by the disappearance of symptoms and by x-ray and gastroscopic evidence. All but one of the patients with duodenal ulcer have been greatly improved or cured, although three patients have required gastroenterostomy because of persistence of obstructive symptoms. The patient with the gastrojejunal ulcer, although improved, has been continued on medical management. The excessive continuous night secretion of gastric juice has been markedly reduced by the vagus section thus providing additional and perhaps conclusive evidence that this abnormality is neurogenic in origin. The striking improvement in these patients is in harmony with the view that gastroduodenal ulcer is a psychosomatic disease, and that the central nervous system affects the stomach via the vagi, probably chiefly through greatly augmenting the secretion of gastric juice.

REFERENCES

1. Dragstedt, L. R.: *Ann. Surg.* 102: 563, 1935; and *Arch. Surg.* 44: 438, 1942.
2. Mann, F. C., and Williamson, C. S.: *Ann. Surg.* 77: 409, 1923.
3. Matthews, W. B., and Dragstedt, L. R.: *Surg., Gynec. & Obst.* 55: 265, 1932.
4. Elman, R., and Hartmann, A. F.: *Arch. Surg.* 23: 1030, 1931.
5. Hay, L. J., Varco, R. L., Code, C. F., and Wangenstein, O. H.: *Surg., Gynec. & Obst.* 75: 170, 1942.
6. Alvarez, W. C.: *Gastroenterology* 1: 534, 1943.
7. Roth, J. A., Ivy, A. C., and Atkinson, A. J.: Chicago, June, 1944, American Medical Association Convention.
8. Dragstedt, L. R., Palmer, W. L., Schafer, P. W., and Hodges, P. C.: *Gastroenterology* 3: 450, 1944.
9. Dragstedt, L. R., and Owens, F. M., Jr.: *Proc. Soc. Exper. Biol. & Med.* 53: 152, 1943.
10. Hartzell, J. B.: *Am. J. Physiol.* 91: 161, 1929.

GASTRIC ULCER AND CANCER

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WHEN the above title is observed, the immediate reaction many will have is that we are planning to offer evidence to support the theory of MacCarty and Broders¹ that cancer of the stomach frequently develops on chronic benign ulcer. This theory would be so difficult to prove and, in fact, would be disputed by so many pathologists that we will do no more than to state that in some ulcerative lesions of the stomach, one portion appears to be definitely benign while another section is definitely malignant. It is not necessary that we accept the possibility of malignant degeneration of chronic gastric ulcer in order to establish in our minds a sound conception of the correct management of ulcer of the stomach. One may even accept the possibility that malignancy is present in the beginning of true cancerous ulcerations and that the benign area or edge frequently observed in early cancer may be nothing more than an inflammatory extension. We are convinced that certain malignant ulcerations may behave like benign ulcer as regards symptoms and response to conservative therapy for a variable period of time only to manifest themselves as obvious cancer at a later observation. That the differential diagnosis between malignant and benign ulcer of the stomach is often difficult or in fact impossible, by the diagnostic methods at our disposal, is accepted. That radical surgery for localized cancer of the stomach appearing benign will result in a greater chance for cure than when the lesion is obviously malignant is evident.

A careful analysis of the data available for a ten-year period at the Massachusetts General Hospital showed that 14 per cent of the patients treated as having benign gastric ulcer proved to have cancer.² All of these lesions at the first observation gave the impression of benign ulcer. Many of these patients responded well to conservative therapy at first, losing their symptoms and regaining previously lost weight. Often the lesion appeared to diminish in size on roentgen and gastroscopic examinations. Occasionally, such an ulcer previously demonstrated by both methods was not recognizable after a month of treatment. This brought about a natural feeling of safety and therefore unnecessary delay in re-examination and the institution of radical surgery. It is difficult to explain the early behavior of some malignant ulcerations of the stomach. The improvement in symptoms and weight of the patient is easier to understand, since with bed rest and nonirritating foods, secondary inflammatory reaction is alleviated. Gastritis disappears and comfort replaces pain, gaseous eructations, nausea, and anorexia. That the actual ulceration appears to diminish in size may be due to the subsidence of inflammation about the ulcer. Possibly the crater may be leveled by granulation tissue or actually by cancer cells.

Received for publication, Oct. 5, 1944.

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In order to arrive at a better diagnosis in the early malignant lesions, we studied our records for common factors pertaining to this group of patients. Helpful information was derived from an analysis of the location of the lesion, the age of the patient, and the duration of his symptoms. Gastric analysis, particularly as regards free acidity, and the size of the ulceration were less impressive. Data concerning the type and radiation of pain and the rate of healing with conservative therapy were of no value.

Holmes and Hampton³ and others have shown that ulceration in the immediate 2 cm. of stomach proximal to the pylorus was prone to be malignant regardless of the size of the lesion. This was true in 65 per cent of our cases. Nearly all ulcers of the greater curvature and the fundus of the stomach are cancer. We found one ulcer in this region to be syphilitic and another that was actually benign. Ulcers involving the anterior or posterior walls proved to be cancer in 20 per cent of the cases. Lesions of the lesser curvature and those of the pylorus itself showed malignancy in 10 per cent. Inasmuch as one-half of all ulcerations of the stomach originate on the lesser curvature, we found that most of our diagnostic errors occurred in lesions of this region.

Ogilvie⁴ and others have previously stressed the importance of indigestion associated with ulceration of the stomach coming on after the age of 40. In our series, we found that patients with ulcerative lesions of the stomach after middle life having had symptoms of less than one year were five times as likely to have cancer as ulcer. If, on the other hand, patients in this age group had had symptoms of five or more years, the reverse was true. Every clinician should seriously consider any patient who appeals for advice about any digestive complaint that begins after the age of 40. The diagnosis of malignancy must be ruled out by all of the aids at our disposal. If an ulcerative lesion of the stomach is demonstrated, radical therapy should be instituted as soon as suitable arrangements can be made. It is in this group particularly, that palliative measures may confuse the true issue and almost under our eyes an early curable cancer may become hopelessly inoperable. These are the victims of indigestion remedies, legally advertised in the newspapers and on the radio. Certainly a time will come when the people will demand protection against these practices. If the profession initiated proceedings against such advertising, we would doubtless have to defend ourselves on the basis of jealousy. Whatever is the best way to meet this situation, we are uncertain but there can be no doubt that hundreds of lives are lost yearly by our lax methods in this direction.

The size of the ulcer may be misleading since cancer was present in two lesions that were less than 1 cm. in diameter. On the other hand, enormous benign lesions giving the clinical impression of unfavorable cancer have been encountered. Actually, the average diameter of malignant ulcers was 2.3 cm. as opposed to 1.7 in benign lesions in our series. In all the ulcers with craters of 2 cm. in diameter, the diagnosis of cancer was established in exactly 50 per cent. It is obvious that we can only surmise that the lesion is benign if it is small

in size, if it is in one of the safer zones, if it is in younger individuals, or if it has occurred in a patient with many years of symptoms.

Free hydrochloric acid was found with equal abundance in the "ulcer-cancer" group as in those with definitely proved benign ulcer. In a parallel group of patients proved to have cancer of the stomach, 60 per cent of them showed no free hydrochloric acid on gastric analysis. We are faced, therefore, with evidence that the presence of free acid is of little help in the differential diagnosis. The absence of free acid, however, is definitely in favor of cancer.

Too much reliance has been placed on the amount of pain associated with gastric ulcerations. The common belief that pain indicates benign ulcer is erroneous. The insidious onset of many cancers of the stomach with its vague symptomatology has contributed to this fallacy. It was evident to us that many of the ulcers in our series that proved to be cancer produced pain that was relieved by food or alkalis in exactly the same manner seen in the benign group. The loss of symptoms with apparent diminution in the size of the lesion on medical treatment, in many instances of early cancer, was particularly disturbing. We are sure that patients with ulcer of the stomach should be kept under close observation. Even if an ulceration has apparently healed after one month of ideal hospital treatment, there should be a careful re-examination four to six weeks afterward. Any evidence of lack of complete healing or return of ulceration should be considered sufficient to warrant early surgery.

Deaths from cancer of the stomach are estimated to aggregate 35,000 in the United States annually.⁵ Comparative studies revealed that for every two persons killed in highway accidents in this country, there were three individuals who died from cancer of the stomach. Thus far, science has not developed an effective treatment for this condition except surgery. So many patients appear for treatment in the hospital when nothing can be offered them that every effort should be made toward earlier diagnoses. Safer surgical methods have increased the operability in the past decade but the percentage of cures has remained unchanged.

Parsons⁶ studied our data on an early series of gastric cancer and found that the resectability was 27 per cent and the operative mortality was 38 per cent. Later, he and Welch⁷ found that resectability had increased to 37 per cent while the operative mortality was reduced to 25 per cent. The five-year respites, which included the operative mortality, had remained practically the same—20 per cent. Needless to say, in the later group, there were many added years of comfortable life. With the increase in surgical effort, there is a definite improvement in the overall results.

In our own group of questionable lesions, it was found that when resection had been done on the diagnosis of benign ulcer only to have the pathologist find that the lesion was cancer, the five-year cure rate increased to 40 per cent. With this in view, we should take a more radical attitude regarding early cancer. It is quite evident that we should include the nodal areas in our resections for all doubtful lesions. This adds little to the hazard of the operation and gives the patient his best chance for cure. It is also clear that we should more frequently do a wider resection. Often a simple total gastrectomy can be safely

done which lends itself to a better elimination of the nodal areas than many subtotal resections. This is particularly true when the lymph nodes in the region of the left gastric vessels appear to be involved. We have practiced Ogilvie's suggestion of including the great omentum in our resections for cancer for several years. It is obvious to us that this structure can be safely eliminated and no serious sequelae have resulted from its absence.

Conservative treatment of gastric ulcer is less satisfactory than it is in duodenal ulcer. Judd and Priestley⁸ have reported that less than 50 per cent of patients with gastric ulcer treated at the Mayo Clinic were satisfied with medical management. In 162 patients treated by surgery, only one was unhappy with the result. In their group of patients treated for benign gastric ulcer, 10 per cent proved to have cancer.

It is not difficult to understand the confusion arising in the minds of clinicians regarding the results of conservative measures in gastric ulcer when we consider the comparative rareness of this lesion. In nearly all clinics, reports will show that duodenal ulcer occurs from seven to ten times as frequently as gastric ulcer. Duodenal lesions respond to conservative therapy in a satisfactory manner in approximately 80 per cent of the patients seen. Only those with complications or intractable pain need be treated by operation. Therefore experience in the treatment of gastric ulcer is more limited and it has taken more time to accumulate sufficient data to arrive at logical conclusions.

Subtotal gastrectomy for gastric ulcer is a safer procedure than it is for duodenal ulcer. The reason is that in gastric ulcer, the duodenum is a normal structure and presents no difficulties in a secure inversion. In duodenal ulcer, however, we are always faced with the problem of the effects of inflammation. This creates some handicap in all these cases and in nearly 25 per cent of them, a real hazard. It has taken time and experience to learn to deal with the situation safely. The mortality rate of gastrectomy for duodenal ulcer will probably always be twice that of the same procedure for gastric ulcer. In a consecutive run of sixty-five patients operated upon by the general staff at our clinic for gastric ulcer, there was one death. This was in a 76-year-old man who succumbed to coronary occlusion one week after the operation.

One should not be tempted to do palliative surgery for gastric ulcer. In a group of twenty-three patients subjected to gastroenterostomy with or without cauterization of the ulcer, there were four who died of cancer of the stomach. This shows that even experienced surgeons cannot tell by the feel or the appearance of a gastric ulcer whether it is benign or malignant.

It is interesting that anastomotic ulcer, which is the most serious and frequent late sequel to partial gastrectomy for duodenal ulcer, does not occur after the same procedure for gastric ulcer.

When one takes into consideration all these data, it seems that we have much to support the conclusion that gastric ulcer should be accepted as primarily a surgical problem. By so doing, we can be assured of a high cure rate for cancer of the stomach in those patients who really have a malignant lesion that appears to be benign. This alone offsets the slight risk associated with adequately executed surgery. Furthermore, the patient with gastric ulcer may expect relief

from his symptoms by this radical procedure and be able, with assurance, to carry his economic load in the community.

We believe that early radical surgery is indicated when a patient appears for treatment if he has an ulcer of the stomach in the prepyloric or fundal regions. If he is over 40 years of age and has had symptoms of less than one year, or if his ulcer is over 2 cm. in diameter, the same advice should be given.

If the patient is young and has a small lesion or if the ulcer is superimposed on symptoms of more than five years' duration, a more conservative attitude is justifiable. This patient should not be treated in an ambulatory fashion, as is common practice in mild or early duodenal ulcer, but should be given the benefit of an adequate hospital regimen. If the ulcer remains even partially unhealed after one month of such therapy or if there is a return of ulceration one month after healing is apparent, then this patient should be urged to submit to surgery.

Actually, when all factors are taken into consideration, this becomes a conservative attitude since it is the most logical course to pursue in our efforts to lower the annual death rate from cancer of the stomach.

REFERENCES

- ✓1. MacCarty, Wm. C., and Broders, A. C.: Chronic Gastric Ulcer and Its Relation to Gastric Carcinoma, Review of 684 Specimens, Arch. Int. Med. 13: 208-223, 1914.
- ✓2. Allen, A. W., and Welch, C. E.: Gastric Ulcer—The Significance of This Diagnosis and Its Relationship to Cancer, Ann. Surg. 114: 498-509, 1941.
- ✓3. Holmes, G. W., and Hampton, A. O.: The Incidence of Cancer in Certain Chronic Ulcerating Lesions of the Stomach, J. A. M. A. 99: 905-909, 1932.
- ✓4. Ogilvie, W. H.: Cancer of the Stomach, Surg., Gynec. & Obst. 68: 295-305, 1939.
5. Livingston, E. M., and Pack, G. T.: End Results in the Treatment of Gastric Cancer, New York, 1939, Paul B. Hoeber, Inc.
6. Parsons, L.: The Operative Curability of Carcinoma of the Stomach, New England J. Med. 209: 1096-1101, 1933.
7. Parsons, L., and Welch, C. E.: The Curability of Cancer of the Stomach, SURGERY 6: 327-338, 1939.
- ✓8. Judd, E. S., and Priestley, J. T.: Treatment of Gastric Ulcer, Surg., Gynec. & Obst. 77: 21-26, 1943.

A SYNTHETIC PREDIGESTED ALIMENT FOR JEJUNOSTOMY FEEDING

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J EJUNOSTOMY for the purpose of alimentation in a patient with obstruction of the digestive tract was first performed more than sixty-five years ago.²³ Originally, this operation was employed for feeding individuals with inoperable cancer of the stomach, but its value soon came to be recognized for various other purposes as well. It was used

The authors wish to thank Miss Henderson of the Diet Kitchen and her staff for their patient cooperation in the preparation of this material; also Mead Johnson and Co. for supplying Amigen; and Burroughs Wellcome and Co. for the Dexin used in this work.

Received for publication, Oct. 11, 1944.

(1) as a palliative procedure for feeding patients in whom oral feedings were either difficult or impossible, such as cases of inoperable obstruction of the esophagus or stomach, caused by acute inflammations or malignancies, or cases of inanition caused by pernicious vomiting of pregnancy; (2) as a preliminary procedure in extensive gastroduodenal and gastrojejunal ulceration, accompanied by marked evidence of alkalosis and refractory to medical treatment; (3) as a prophylactic measure for the relief of certain postoperative complications following surgery of the stomach, such as gastric dilatation and duodenal fistula arising from suture insufficiency, the jejunostomy being complementary (that is, made coincidentally with the major operation) or supplementary (that is, made subsequently to it); and (4) as a definitive procedure for primary gastroduodenal ulcer and for marginal ulcer secondary to gastroenterostomy—a use which was in vogue for a time, but has since lost its popularity. A detailed discussion of the numerous applications of jejunostomy is presented in a historical review of the subject, published elsewhere.²⁰

Apart from its use as a palliative procedure, the most important application of jejunostomy is as an adjuvant to surgery, in order to correct certain disturbances in physiology which are attendant upon the patient's condition prior or subsequent to operation. An individual with a high obstruction of long standing, accompanied by persistent vomiting and prolonged starvation, is likely to be dehydrated, in acid-base imbalance, in negative protein balance reflected by a hypoproteinemia, and in a state of avitaminosis apart from a general state of inanition. These disturbances increase the risk of any radical operation; their preoperative correction will diminish the incidence of postoperative mortality and morbidity. Derangements in water and electrolyte equilibria can be corrected by intravenous therapy, but loss in body weight and marked hypoproteinemia may respond only to suitable alimentation over a period of one month or six weeks. In addition to the physical improvement of the patient resulting from such feeding, there will also be a substantial improvement in the local pathologic lesions. Large gastroduodenal and jejuno-marginal ulcers may be greatly reduced in size by protracted jejunal feeding. This occurs as a consequence of the simultaneous operation of several factors: (1) a reduction in the acidity of gastric contents,^{13, 18, 21, 28} due to an inhibition of the secretory process, or augmentation of neutralization by regurgitated intestinal contents, or both; (2) the absence of mechanical irritation of the ulcer which occurs during oral ingestion; (3) a reduction in motor activity of the stomach, as a consequence of the frequent or continuous administration into the jejunum of a diet of high caloric value; and (4) the progressive elimination of gastric retention, by restoration of gastroduodenal continuity as the local inflammatory reaction and edema subside. Such local improvement due to a preliminary jejunostomy converts a previously inoperable condition into one in which a subtotal gastrectomy may be performed with a minimum of risk.

The value of a complementary jejunostomy in postoperative management is no less than its value as a preliminary procedure. Not only is it possible, by means of jejunal feeding, to place the patient on a high caloric and fluid intake within a short time after gastric resection or gastroenterostomy, but he can be so maintained for weeks or even months

without resorting to parenteral therapy. The efficacy of proper post-operative alimentation in ulcer patients has been objectively demonstrated by the carefully controlled, preliminary study of Mulholland, Co Tui, Wright, and Vinci.¹⁰ In this work it was reported that the convalescence of duodenal ulcer patients, maintained postoperatively on oro-jejunal tube feeding of a pabulum high in amino-nitrogen, was more rapid and uneventful than that of a control group of patients not fed by tube. Furthermore, these observers found that the enteric administration of amino acids resulted in more effective utilization, as shown by nitrogen balance studies, than was obtained by their intravenous injection.

The foregoing applications and advantages of jejunostomy feeding are so striking that one wonders why the procedure has not gained wider use. There are several reasons for this. When jejunostomy was first employed, it was accompanied by certain postoperative complications: loss of intestinal contents through incompetence of the jejunal stoma, the persistence of a jejunal fistula after withdrawal of the enterostomy tube, and the frequent occurrence of intestinal obstruction due to technical imperfections associated with the Witzel type of jejunostomy. These difficulties have since been obviated by improvements in surgical technique. Another reason for the unpopularity of jejunal alimentation was the distention, nausea, vomiting, cramps, diarrhea, and enteritis, which frequently accompanied it.²⁰ Colp and Druckerman,⁶ in a series of patients upon whom jejunostomy was performed for alimentation, reported that about 10 per cent of the patients complained of diarrhea and cramps. The nutrient material used for these cases was a standard one which had been recommended specifically for this purpose, the Scott-Ivy pabulum. It has been generally accepted that these distressing gastroenteric symptoms may be caused either by physical factors or by a group of distinctly chemical ones. Scott, Holinger, and Ivy²² themselves comment on the great likelihood of occurrence of diarrhea and enteritis. The milder of these symptoms have been clearly associated with physical factors like the temporary engorgement of the small intestine with food material. These are easily prevented by control of the rate of drip administration, using either an efficient drip apparatus or a motor-activated pumping device such as has been described by Einhorn,⁹ Mensing,¹⁷ and Wolfer.²⁸ Massive feedings (that is, the periodic injection of 100 c.c. or more during a ten- to fifteen-minute interval, followed by a rest period for the remainder of one hour) are also feasible, without provoking these mild disturbances. It is essential, however, that such massive feedings be started at a lower rate than this, and be gradually increased day by day to a maximum compatible with the patient's tolerance. Following such adaptation, Stewart²⁴ has injected as much as 400 c.c. at one time, though it is likely that his patient was not always free of distress. Marked deviation in temperature of the dietary material from 37° C. has also been thought to be an irritant factor of significance, and many reports specify precautions on this score.

Cramps and diarrhea, however, have constituted a more serious complication and possibly a more frequent one, as evidenced by the widespread prescription of opium or similar medication. It has been generally accepted that these disturbances are caused by one or more of the

constituents of the jejunal aliment. The importance of unemulsified fat in this connection is particularly marked; attention was called to it by Busch⁵ as far back as 1858, twenty years before the first surgical jejunostomy was performed. Busch employed jejunal feedings for over twenty-one weeks on a woman with a natural jejunostomy, resulting from the severance of the small bowel when a bull gored her. As a result of this mode of feeding, the patient gained twenty pounds (30 per cent) in body weight. An excessively high osmotic pressure may also be a contributing factor to jejunal irritation, since it will require considerable time for the small bowel to dilute the aliment sufficiently to prevent osmotic stimulation of the neuromuscular mechanism. These complications arising from the food material itself seem to have been a major deterrent to extensive use of a surgical procedure which is of considerable potential advantage in the management of surgical cases, and simple and safe as well. In our own observation of the routine handling of jejunostomy patients, we have repeatedly seen the abandonment of jejunal alimentation because of cramps and diarrhea, in spite of the continued need of nutritional improvement. Wangenstein, in his book on *Intestinal Obstructions*,²⁷ says: "The experience of this clinic suggests that the ideal formula for feeding through an enterostomy has not been found. Trial and error, with temporary periods of alimentation by the intravenous route, until the proper adjustment is made, continues to be the method that must be employed. . . ." In this same connection, Wolfer²⁸ states that the major proportion of previous efforts at jejunostomy feeding has been disappointing because of an inadequate understanding of the physiologic principles involved. In view of these statements and our own confirmatory experience, we have devised a new diet which conforms to the physiologic and other requirements that have been brought to light by the cumulative experience of sixty-five years of trial and tribulation.

COMPOSITION OF THE ALIMENT

For jejunal feeding, the aliment must be very easily digestible or even predigested. This is necessary because salivary and gastric digestion are completely eliminated, and pancreatic and intestinal digestion are lessened, the latter as a consequence of decreased stimulation of the corresponding glands and the reduced time of contact of these secretions with the aliment. Extensive predigestion is important also for a maximum of absorption. Wangenstein²⁷ pointed out that the actual caloric value of the Scott-Ivy pabulum is considerably less than the calculated value because of its incomplete digestion and consequent incomplete absorption. Scott and Ivy²¹ realized this and attempted to obviate the loss by predigesting the mixture with gastric juice and pancreatin, but the product was too irritating to be tolerated. Any factors which may irritate the bowel must be excluded from an enteric aliment. Its pH should be about 6.0. Its osmotic pressure must not be too much above isotonicity, since the reduction in this property which normally results from dilution with the digestive secretions after oral feeding is greatly lessened in jejunal alimentation. In order to satisfy these requirements the various constituents of the new aliment were supplied in the following ways.

1. *Protein*.—The nitrogenous component of the enteric aliment should contain no molecules larger than tripeptides. It must, however, contain adequate amounts of the ten essential amino acids, free or combined. These requirements are met by Amigen,* an enzymatic digest of purified casein and pork pancreas which contains di- and tripeptides and amino acids (including tryptophan). McGee and Emery¹⁶ have reported that this preparation, when placed directly into the human small intestine by the balloon intubation technique, was completely absorbed in fifteen to twenty-five minutes, whereas unhydrolyzed casein required forty to fifty minutes. The proportion of the total caloric intake derived from protein in several well-known feeding mixtures (Kirschner,¹⁴ Scott and Ivy,²¹ Walters and Hartman²⁶) ranges from 6 to 16 per cent (Table I). In the predigested aliment, about 26 per cent of the total caloric intake comes from this source. Based on a daily intake of 2,400 cal. this corresponds to somewhat less than 160 Gm. of pure protein per day, or about 200 Gm. of hydrolyzed casein.† This value is far below the maximum which can be tolerated, for Brunshwig, Clark, and Corbin⁴ were able to inject intravenously 150 Gm. of hydrolyzed casein per day in a 50 kg. patient for ten days without any disturbance. Also, Elman, Weiner, and Bradley¹¹ have injected as much as 300 Gm. per day in each of two patients without difficulty, though their observations extended for only three consecutive days.

TABLE I

COMPARISON OF SEVERAL JEJUNOSTOMY FEEDING MIXTURES WITH REGARD TO THE RELATIVE AMOUNTS OF CARBOHYDRATE, PROTEIN, AND FAT

FORMULA DEVISED BY	AMOUNT (PER LITER OF THE MIXTURE)							
	CARBOHY- DRATE		PROTEIN		FAT		TOTAL	
	GM.	CAL. %	GM.	CAL. %	GM.	CAL. %	GM.	CAL. %
Kirschner*	94	376 (37)	35	140 (14)	55	495 (49)	184	1011 (100)
Scott and Ivy	81	324 (38)	35	140 (16)	43	387 (46)	159	851 (100)
Walters-Hartman								
1st day	65	260 (47)	8	32 (6)	29	261 (47)	102	553 (100)
2nd day	90	360 (44)	21	84 (10)	42	378 (46)	153	822 (100)
3rd day	97	388 (43)	25	100 (11)	46	414 (46)	168	902 (100)
6th day	101	404 (37)	33	132 (12)	63	567 (51)	197	1103 (100)
Hollander, Rosenak and Colp	152	607 (60)	66	265 (26)	16	139 (14)	234	1011 (100)

*Calculated with the aid of Sherman's tables of the caloric value of foods.

Such a high proportion of protein nitrogen is desirable, not only to prevent the further depletion of the body stores of protein, but also to replenish the tissue protein and plasma albumen previously lost by

*Manufactured by Mead Johnson and Co.

†The total nitrogen content of Amigen is given as 12.0 per cent, and this corresponds to 75 per cent of protein. Hence, to obtain 150 Gm. of protein, apart from that in the cream, we must use 200 Gm. of the hydrolyzed casein as purchased. It is usually stated, however, that 1.2 Gm. of Amigen is equivalent to 1.0 Gm. of protein, which corresponds to a protein content of 83 per cent. The discrepancy between this value and 75 per cent probably arises from the fact that the former has been calculated on the basis of a dry, ash-free preparation, instead of "as purchased." This is suggested by the following consideration. The moisture content of Amigen is given as 4.0 per cent and the total ash as 5.5 per cent; hence the nitrogen value becomes 13.3 per cent (that is, $12.0 \times \frac{100}{100 - (4.0 + 5.5)}$). Multiplying this by the usual factor of 6.25 for the conversion of nitrogen to protein, we obtain 83 per cent.

starvation and hemorrhage. Rapid regeneration of body proteins means better healing of tissues and prevention of wound dehiscence. Rapid correction of the hypoproteinemia may diminish the edematous swelling of an obstructed gastroenteric stoma or pyloric orifice. The relative amounts of amino acids utilized for the replacement of tissue and blood proteins are about 25 to 1, depending on the degree of depletion of the body and plasma stores, and the individual's ability to resynthesize the latter. Hence, only about one-twenty-sixth of the total daily intake of nitrogen is likely to be utilized by the body for the more urgent of these two purposes, the restoration of the plasma protein level, assuming that the combined intake of carbohydrate and fat is great enough to spare the amino acids from deamination.

2. *Carbohydrate*.—The requirement of predigestion for the carbohydrate constituent might be met by the use of glucose. However, Scott and Ivy,²¹ Wolfer,²⁸ and others reported that glucose frequently causes diarrhea, probably as a result of fermentation, but that cane sugar is better tolerated. Some surgeons have recommended a reduction in sugar content for any patient in whom such difficulties are encountered; it was our aim, however, to prevent the occurrence of fermentation so that changes in composition from patient to patient will not be necessary. This end was attained by the use of Dexin,* an enzymatic digest of cereal starch, prepared with barley malt, which consists solely of dextrans (75 per cent) and maltose (25 per cent). Another advantage in the use of a starch hydrolysate is that it elevates the osmotic pressure much less than will a quantity of a simple sugar having the same caloric value. About 60 per cent of the caloric value of the aliment is derived from the carbohydrate, a proportion higher than in any of the others shown in Table I. The feeding of a large proportion of carbohydrate is of importance in order to replace the depleted glycogen stores of the liver. Furthermore, by reason of its protein-sparing action, it insures a maximum utilization of the amino acids for the building of blood and tissue proteins. Sixty per cent of carbohydrate is considerably more than is required for these purposes, but this large proportion is a consequence of the relatively small amount of fat which has been employed.

3. *Fat*.—The influence of fat in causing cramps and diarrhea has already been pointed out. Even if the motility of the small bowel is increased somewhat (though not to the extent of causing diarrhea), the consequent decrease in absorption of nutrient material may result in a loss of efficiency of utilization. Furthermore, the presence of fat in the upper part of the small intestine induces a decrease in gastric motility, as a result of enterogastrone secretion, and therefore in gastric emptying. To minimize this reaction, Wangenstein²⁷ recommended that the fat content be kept below two-sevenths of the total *weight* of the nutrient. Based on *caloric value*, this is equivalent to 47 per cent of the total intake, a value which roughly characterizes all of the previous mixtures (Table I). This percentage seems to us to be excessively high. Hence, the proportion of calories derived from fat in the synthetic aliment was made about one-third of this value. It was felt that predigestion of fat is not important, but it is essential that this nutrient component contain a significant quantity of unsaturated fatty acids and

*Manufactured by Burroughs Wellcome and Co.

that it can be emulsified easily. Thin cream (18.5 per cent fat content) possesses these qualifications, and it has proved satisfactory for our purpose.

4. *Inorganic Constituents.*—The inorganic requirement of a well-balanced diet is not entirely taken care of by the combined mineral content of the Amigen, Dexin, and cream. The ash content of Amigen is given as 5.5 per cent; for thin cream, 0.43 per cent; and for Dexin, 0.25 per cent; chemical analyses of the ash were available only for the first two. The deficiency in the inorganic elements, as judged by accepted standards, is made up by means of a salt mixture, the composition of which was established in the following way:

Sodium chloride: No fixed dietary standard of salt requirement can be established because of its complex physiologic relations. The normal daily intake, as calculated from the sodium and chlorine data of a survey of 150 American dietaries,²³ varied between 0.5 and 9.7 Gm. NaCl. but this was exclusive of additional table salt used as flavoring, which could not be estimated in this survey. The average for all the dietaries was 4.8 Gm. per man per day. To their jejunostomy pabulum, Scott and Ivy added 6 to 10 Gm. of NaCl per day in addition to that derived from the other constituents, but they specified that the amount must not exceed this because of the possibility of a salt edema. A 10 Gm. limit was also set by Elman and Weiner¹⁰ as a supplement in connection with the intravenous administration of amino acids. Neither of these groups of workers, however, intended this amount of salt to compensate for an alkalosis or hypochloremia, secondary to the loss of digestive secretions. In view of the wide variability in the daily amount of saline which may be needed by surgical patients for these latter purposes, the excess requirement was not included in the salt mixture for the aliment. Instead, it was estimated for each individual case and was supplied independently of that contained in the diet, either parenterally or by jejunostomy. Hence, the total daily NaCl content of the aliment was set at 10 Gm. The salt content of the protein and fat constituents was estimated to be around 5.2 Gm. Therefore, 4.8 Gm. of NaCl per 2,400 Cal. must be added to the jejunostomy aliment by way of the salt mixture.

Potassium: The element potassium also is recognized as a dietary essential, without any estimated "requirement" being attainable. The average daily intake of the 150 American dietaries was 3.4 Gm. of potassium (range, 1.4 to 6.5 Gm.), whereas the amount of this element derived from the Amigen and cream is only 0.9 Gm. per 2,400 Cal. Hence, the daily allotment of salt mixture should include 2.5 Gm. of potassium; this is introduced in the form of KCl (4.8 Gm. per 2,400 Cal.).

Magnesium: The amount of magnesium reported in the dietary survey varied between 0.14 and 0.67 Gm. per day, with a mean of 0.34 Gm. Only about one-third of this amount is contributed by the nutrient materials of the jejunostomy diet; the balance (0.22 Gm.) is supplied in the salt mixture, in the form of the hydrated sulfate (2.2 Gm. of Epsom salts for every 2,400 Cal. of aliment).

Calcium: The Committee on Foods and Nutrition of the National Research Council has recommended a daily intake of 0.8 Gm. of calcium for all adults, except during pregnancy and lactation, when the specification is about doubled. The calcium derived from the cream

and Amigen is 0.37 Gm.; this leaves a deficit of 0.43 Gm. of calcium, which is made up by 4.8 Gm. of calcium gluconate (monohydrate, U.S.P. XI) in the salt mixture.

Iron, copper, and other metals: The National Research Council's recommendation for the daily requirement of iron in normal adults is 12 mg. Inasmuch as the Amigen alone contributes 41 mg., none of this element need be added to the salt mixture. Likewise for copper, since the 4 mg. contributed by this constituent is adequate for erythrocyte and hemoglobin formation in normal individuals. The presence of these two metals obviates, in all probability, the need for manganese and cobalt. In the event of a marked anemia, such as might result from a bleeding ulcer, additional quantities of iron and copper should be prescribed.

Phosphorus: The mean phosphorus content of the dietaries cited by Sherman varies between 0.6 and 2.8 Gm., with a mean of 1.6 Gm. per day. Therefore the quantity of phosphorus (about 2.0 Gm.) supplied by the Amigen and cream is sufficient, and no additional phosphorus need be included. However, some alkali phosphate was added to the salt mixture in order to adjust the acidity of the aliment from a pH around 5.5, which characterizes Amigen and Dexin, to a value of 6.0 to 6.5. For this purpose, 7 Gm. of secondary sodium phosphate (Na_2HPO_4 , U.S.P., dried) per 2,400 Cal. was found to be sufficient.

5. *Vitamins.*—A suitable supply of vitamins is essential in general, but particularly in patients with peptic ulcer, who are likely to be markedly deficient in this respect. The daily allowances recommended by the National Research Council, Committee on Foods and Nutrition, however, make no provision for such deficits. Therefore, a minimum of twice the amounts specified for a 70 kg. male at the 2,500 Cal. level was employed for the aliment. The adjusted values are as follows: vitamin A, 10,000 IU (6 mg. β -carotene); vitamin D, 800 IU; ascorbic acid, 3,000 IU (150 mg.); thiamin, 1,000 IU (3 mg.); riboflavin, 4.4 mg.; nicotinic acid, 30 mg. These accessory factors were given in the form of halibut liver oil and a vitamin B-complex mixture,* which also contains pyridoxine and the filtrate factor. In addition to these quantities, however, the usual therapeutic doses should be administered for several days prior to the operation for jejunostomy.

6. *Calories.*—The foregoing calculations have presumed a total caloric intake of 2,400 Cal. per day. This is slightly higher than that usually recommended for a sedentary young or middle-aged man, for whom Sherman prescribes 2,000 to 2,200 Cal. The same level has been recommended for jejunostomy feeding by Wangensteen. Kirschner's¹⁴ diet contains about 2,000 Cal. also. Walters and Hartman²⁶ maintained the caloric level at 1,300 from the third through the fifth postoperative day, and thereafter raised it to 2,500 Cal. by changing the proportions as well as the amounts of the several constituents. It must be remembered that a febrile reaction, following the operation, means an increased metabolism; the resultant increase in caloric requirement is usually estimated at 10 per cent per degree of fever. Based on these considerations, 2,400 Cal. was set as a daily standard for jejunal alimentation in the present work. Such feeding was started at a level much lower than this, because of bowel intolerance to large volumes of material post-

*Blexin, manufactured by International Vitamin Corp.

operatively. However, following a suitable period of adaptation, it was often possible to administer 3,000 Cal. or more per day by means of the predigested aliment.

7. *Water*.—Best and Taylor² state that the normal adult water requirement under ordinary circumstances is around 2,500 c.c. daily. Complete metabolism of the protein, carbohydrate, and fat in 2,400 Cal. of the predigested aliment will furnish about 300 c.c. of water. Empirically, however, we found that a final concentration equivalent to 1 Cal. per cubic centimeter was adequate for routine purposes. Additional fluid required in cases of dehydration or thirst may be supplied parenterally, immediately after the operation, or by the addition of physiologic saline solution to the aliment. A concentration as high as 1.5 Cal. per cubic centimeter was tolerated without difficulty both by dogs and by patients, but this upper level reduces the basal water intake to an undesirable extent. Furthermore, the consistency of the mixture at the lower concentration is sufficiently fluid so that clogging of the dispensing apparatus does not occur. The osmotic pressure of the aliment is substantially greater than the isotonic value, but the absence of any complications attending the use of this concentration suggests that the degree of hypertonicity is low enough to obviate excessive stimulation of bowel motility. However, this osmotic concentration factor is being given further investigation.

PREPARATION AND ADMINISTRATION OF THE JEJUNAL ALIMENT

Amounts of the amino acids, carbohydrates, and salt mixture, sufficient to make a liter of the diet (Table II) were weighed out and dissolved in warm tap water without stirring. The mixture, possessing a volume about 900 c.c.* was transferred to a milk bottle, capped, and sterilized. After cooling to below 10° C., the requisite amounts of the vitamin preparations were added, the ascorbic acid being first dissolved in a small amount of sterile water. The preparation was kept in the refrigerator until required for use, when it was warmed to about body temperature and the cream added with vigorous shaking. Scott and Ivy,²¹ Boekus,³ and others call attention to the need for warming the

TABLE II
COMPOSITION OF THE PREDIGESTED ALIMENT

	AMOUNT	
	PER LITER	PER 2,400 CAL.
Water	760 c.c.	1,824 c.c.
Amigen	85 Gm.	204 Gm.
Dexin	150 Gm.	360 Gm.
Cream (18.5 per cent; density = 1.01 at 19° C.)	85 c.c.	204 c.c.
Salt mixture [*]	10 Gm.	24 Gm.
Vitamins (minimum amounts)		
Halibut liver oil†	0.33 c.c.	0.8 c.c.
Blexin†	5.8 c.c.	14.0 c.c.
Ascorbic acid	63 mg.	150 mg.

*The salt mixture is prepared in the following proportions

NaCl	100 Gm.	4.8 Gm.
KCl	100 Gm.	4.8 Gm.
MgSO ₄ · 7H ₂ O	46 Gm.	2.2 Gm.
Ca gluconate · H ₂ O	100 Gm.	4.8 Gm.
Na ₂ HPO ₄ dried	160 Gm.	7.0 Gm. (ca.)

†International Vitamin Corp.

*As prepared in our diet kitchen, the material is made up in larger quantities than this and distributed among a number of bottles, each containing about 900 c.c. of the mixture.

material before administration. Trial experiments in this laboratory, however, have shown that the aliment is well tolerated in dogs with healthy gastrointestinal tracts, at temperatures between 20 and 40° C., provided that the rate of administration is properly controlled. However, for clinical use it is our practice to warm the material to 37° C. before placing it into the dispensing apparatus.

The aliment was administered by means of a gravity drip apparatus, provided with a needle valve at the air inlet, as described elsewhere.⁷ By means of this valve, the speed of injection can be kept relatively uniform, at an average rate below 200 c.c. per hour. The cream is well emulsified and will not separate if the mixture is gently agitated by air flowing into the drip reservoir through a Mariotte tube. If the cream does separate because of interrupted use of the apparatus, it can be redistributed by gentle shaking of the reservoir. The mixture is more fluid than preparations containing starchy or mealy substances, and therefore it does not clog the rubber tube or orifices of the apparatus.

EFFICACY OF THE PREDIGESTED ALIMENT

The value of any jejunal aliment must be gauged first of all by the absence of cramps, diarrhea, and other disturbing symptoms during its administration; second, by its ability to maintain or increase body weight; and third, by its efficiency in correcting dehydration, hypoproteinemia, and alkalosis. In the present report, experimental and clinical data concerning the first two of these criteria are presented. A systematic investigation of the efficiency of the predigested diet in correcting water, electrolyte, and protein imbalances has been left for subsequent study.

Tolerance to the predigested aliment was first established by oral administration to two dogs (Dogs 131 and 142) without jejunal fistula. Both animals had lost some weight following gastric operations for other purposes, and this loss was augmented by limited food intake. They were then given the jejunal aliment by mouth, one feeding each day, for a period of thirty-eight days. Two other dogs were provided with a jejunal fistula by the Mann-Bollman¹⁵ technique, which uses a three-to four-inch piece of ileum connecting the jejunum with the skin, to form a T type of jejunostomy. One of these animals (Dog 67) lost some weight prior to, and immediately after, the operation, before jejunal alimentation was instituted; the other (Dog 154) maintained its weight over this pre-experimental period. Jejunal feeding of the predigested mixture to the first dog was continued for five and one-half weeks, and to the second for over eight weeks. During these periods, various modifications in the conditions of feeding (quantity per day, rate of administration, temperature, etc.) were made for experimental purposes, but none of them were significant as regards body weight changes.

The quantities fed, the duration of feeding, and the weight change are indicated in Table III. The average daily intake of the diet, as presented in the last column, was calculated on the basis of the actual number of calories given the animal each day during the period of observation. In order to calculate this "per kilogram body weight," we used a "normal" weight which had been estimated from a series of weights taken prior to operation; during this preoperative period the animals had been kept on a stock diet and in excellent nutritional con-

TABLE III

SUMMARY OF OBSERVATIONS ON THE ADMINISTRATION OF THE PREDIGESTED ALIMENT

SUBJECT	METHOD OF FEEDING	DURATION OF FEEDING (DAYS)	BODY WEIGHT (KG.)				AVERAGE INTAKE OF ALIMENT† PER CAL. PER KG. PER DAY
			"NORMAL"***	MINIMUM (AT START OF ALIMENTATION)	FINAL	CHANGE (PER CENT)	
Dog 131	Oral	38	12.0	6.3	7.4	1.1 (17%)	85
Dog 142	Oral	38	14.0	10.0	10.2	0.2 (2%)	70
Dog 67	Jej.	38	10.0	8.0	8.4	0.4 (5%)	98
Dog 154	Jej.	58	11.4	11.4	12.1	0.7 (6%)	83.5
Patient 517,369	Jej.	34	68.2	55.0	61.8	6.8 (12.4%)	2,200‡

*For the dogs, this was estimated from the preoperative weight over several months. For the patient, it was based on his own estimate.

†This average was calculated on the basis of the "normal" body weight and the actual amounts given each day during the period of observation.

‡This value represents the total daily intake, and includes an average of 334 Cal. per day of milk given by intragastric drip.

dition. In this connection it should be noted that the basal metabolic rate for dogs, on the average, is estimated at 35 Cal. per kilogram body weight per day, for a 12 to 13 kg. animal.¹ However, the actual maintenance requirement, without increase of body weight, of a moderately active adult dog is usually set around 80 Cal. per kilogram per day.⁸ The average caloric intake of the four dogs maintained on the predigested aliment varied between 70 and 98 Cal. per kilogram per day. At these levels the initial body weight was maintained or increased over the periods of alimentation, the response varying with the previous condition of the animal as well as the completeness of absorption of the foodstuff.

In all of the animal experiments, the concentration of the aliment was kept constant, at 1 Cal. per cubic centimeter. The jejunostomy dogs received the material by continuous drip, usually in three feedings per day. These feeding periods lasted one to two and one-half hours each, with an interval of one hour between. In Dog 67, the initial rate was 200 c.c. per hour, but this was increased to 260 c.c. on the second day. Thereafter it varied between 200 and 340 c.c. per hour. At the week end, jejunostomy feeding was discontinued and the total amount of material was fed orally. In the second animal (Dog 154) it was necessary to reduce the initial rate of drip administration to 150 c.c. per hour, because of a lower tolerance. During the third day, it was increased to 200 c.c. On the fifth day the rate was stepped up further to 250 c.c., following which it varied between this and the initial value. On the fifteenth day, the dog passed a watery stool and vomited. Episodes of vomiting occurred repeatedly for several days. There was a sudden weight loss of about 1 kg., and the experiment was discontinued temporarily. Throughout this episode, however, the stools were normal or "semiformed." The dog was kept on a bread and milk diet for the following ten days, during which time the vomiting stopped completely and 1 kg. of weight was regained. At this point jejunostomy feedings were resumed and were continued for forty days thereafter. During this second experimental period, the mode of administration was changed

from the drip to the massive injection technique, 160 c.c. being injected over an interval of fifteen minutes or less; this was repeated at hourly intervals. Oral feedings were given only during the week ends. Throughout this period no gastrointestinal disturbances occurred and the animal continued to gain in weight.

Apart from an occasional episode of loose stool in the earlier days of experimentation with Dog 67, and the one incident just referred to in Dog 154, there was never any evidence of diarrhea or abdominal pain in any of these animals. While the absence of such disturbing symptoms may be taken as a matter of course during oral feeding, their absence during the jejunostomy experiments clearly indicated that the aliment was nonirritating. The several loose stools were suspected of being associated with the presence of a contaminating organism in the aliment. Following the institution of routine daily sterilization of the drip apparatus, as well as of the aliment, this minor disturbance disappeared almost entirely. Vomiting never occurred as a consequence of oral feeding, but it was noted occasionally during the early trials of jejunal alimentation. This disturbance was clearly a consequence of an excessive rate of feeding, for it disappeared immediately when the rate was reduced. It is interesting to note, in this connection, the statement by Elman and Lischer¹² that the intravenous administration of an amino acid mixture to human beings causes vomiting when the rate exceeds 25 Gm. per hour.

Gross response of patients to the synthetic diet was established by its routine administration to eight ward patients. One of these was a jejunostomy preliminary to gastric resection; the others were complementary jejunostomies, having been performed simultaneously with subtotal gastrectomies. Two of these cases were followed more carefully than the other six, but in none of them was a systematic study made of the clinical efficacy of the new feeding mixture. The total duration of jejunal alimentation varied from six to forty-eight days, depending on the needs of the patient. The aliment was administered by the drip technique; sometimes saline solution was added, especially during the first postoperative days, when it was felt that additional water and salt were desirable. The rate of administration was always low during the first days (30 to 60 c.c. per hour) and was increased gradually thereafter to a maximum around 125 c.c. per hour. However, no systematic procedure was followed in these preliminary studies, and on occasion the drip rate was as great as 200 or even 300 c.c. per hour. Usually, the total quantity administered in twenty-four hours fell short of the goal of 2,400 Cal., because of uncontrolled variations in drip rate and intermittent discontinuance of the drip feeding, resulting from the shortage of nursing service. For this reason, some mechanical device for dispensing the material at a controlled rate is highly desirable.

All patients receiving the synthetic aliment for any significant length of time gave ample evidence of an improvement in general nutritive condition and in the chemistry of the tissue fluids. One of the two patients given special attention (No. 518919) had had a gastroenterostomy performed for an inoperable cancer infiltrating the duodenum and the head of the pancreas. During eighteen days immediately following operation, the patient was maintained on jejunal alimentation without

supplementary oral feeding, and gained seven and one-half pounds. The other (No. 517369) was a man with a history of duodenal ulcer of fifteen years' duration. An exploratory laparotomy revealed a duodenal ulcer so extensive that a subtotal gastrectomy was impossible; therefore, a preliminary jejunostomy was performed for alimentation and gastric rest. For three and one-half weeks thereafter, the patient continued to suffer violent distress and was generally uncooperative, so that although jejunal feeding was employed, it could be pursued for only part of this period and then unsystematically. By the middle of the fourth week, when his weight had dropped to the lowest observed during his period of hospitalization (121 pounds), we were able to induce a spirit of cooperation by confiding to him the investigative nature of our work. In a short time he was able to fill and control the drip apparatus himself, so that the feeding process was considerably more efficient than with any of the previous subjects. The average jejunal intake of synthetic aliment over a period of thirty-four days was about 1,850 c.c. per day; the highest single value was 4,500 c.c. per day, which appeared to be the limit of his tolerance. In addition to this, he was given about 500 c.c. (334 Cal.) of milk per day by intragastric drip, for the purpose of intragastric neutralization. Hence, his average daily intake of nutrient was almost 2,200 Cal, which resulted in a gain of fifteen pounds in weight in the course of five weeks. The pain subsided shortly after jejunal alimentation became regular. Following this period of gastric rest, a second exploration was performed, two months after the first exploratory operation. There was a striking reduction in the size of the ulcer and in the inflammatory reaction about it. A subtotal resection was performed with ease, and the postoperative course was uneventful.

Neither of these two patients experienced cramps or diarrhea, although the first had one episode of loose stools. In fact, actual diarrhea occurred in only one of the eight patients fed with the synthetic aliment (No. 518563), a patient with carcinoma of the pancreas and a functional liver impairment, who was maintained in this way for fifteen days following gastroenterostomy and jejunostomy. Twice during this period (on the fifth and sixth days) this patient experienced diarrhea, and there was a single loose stool on the eighth day and a single episode of vomiting on the eleventh. Abdominal cramps did not occur in this patient but they were reported in two others. In one of these they occurred, without any other disturbance, at the end of a ten-day period of alimentation. At this time the jejunal intake of 2,000 to 2,400 c.c. per day was being supplemented orally with a soft diet. In the second patient they occurred twice, on different days. However, one of these episodes occurred when the patient was receiving no jejunal alimentation at all; the second episode occurred at the end of a three-day period of distention and vomiting, during which the jejunal intake was never greater than 840 c.c. per day. The succeeding six days were unaccompanied by vomiting, cramps, etc., even though the intake on one of these days was greater than 2,600 c.c. Consequently, the disturbances on both these days must be attributed to a cause other than the composition of the jejunal aliment. Vomiting, in association with jejunal feeding, occurred once with each of two patients, and four times (on two suc-

cessive days) with a third, but these symptoms disappeared as soon as the rate of administration was reduced to a more tolerable level. Subsequent gradual increase of the rate of drip was always well tolerated, and some of our patients were able to take as much as 300 c.c. per hour with no reaction worse than a feeling of fullness. This is consistent with our dog experiments, in which as much as 340 c.c. per hour was administered without untoward effects.

DISCUSSION

Our major problem in the present work was to develop a nutritionally adequate diet for jejunal alimentation which could be tolerated without the disturbing gastrointestinal symptoms which have attended the use of previous formulae for this purpose. An analysis of the factors which are important in the composition of such an enteric aliment indicated that it must be nonirritating and very easily digestible or predigested. This calls for a suitable adjustment of the pH of the nutrient material, avoidance of an excessively high osmotic pressure, and the omission of fruit juice as a source of vitamins. The daily caloric intake should be high enough to effect an increase in body weight. The calories must be distributed among the major nutritive elements in such a way that the proportion of protein calories is fairly high and fat calories low. Previous workers recognized the need for a low fat intake in order to prevent the cramps and diarrhea, but in spite of this, several well-known enteric feeding mixtures contain a very high proportion of calories from this source. Furthermore, the fat must be supplied in a well-emulsified form; thin cream has been found excellent for this purpose. As for the protein, a mixture of amino acids and simple polypeptides afforded an adequate degree of predigestion without sacrifice of any of the essential amino acids. As a source of carbohydrate, glucose must be excluded because its fermentation may cause diarrhea. The use of cane sugar alone is also undesirable, because it would result in an excessive elevation of osmotic pressure. In the present work, a mixture of maltose and dextrans proved to be satisfactory. Provision must be made for all the essential vitamins and minerals, especially an adequate supply of NaCl to maintain water and salt balance, and of iron and copper for hemoglobin formation. If avitaminosis, alkalosis, anhydremia, or anemia are present, the jejunal supply of these factors must be supplemented parenterally or by the jejunal route. Proper sterilization of the aliment (before the addition of the vitamins) and of the drip apparatus is a factor of considerable magnitude in relation to the prevention of a possible enteritis. And finally, proper control of the rate of administration is of paramount importance. Unless the feeding is slow enough, the aliment may cause nausea and vomiting. For this reason, a satisfactory jejunal aliment must be of fairly thin consistency, so as to ensure a more or less even flow of material from the drip apparatus into the jejunum. A mechanical dispenser is to be preferred to a drip apparatus, but as yet we have been unable to obtain one for our purpose.

After several experimental mixtures had been tried, a preparation was finally evolved which conformed with these requirements. This synthetic predigested aliment was then given to dogs, by the oral and jejunal routes, in order to study its efficacy in regard to maintenance of

body weight, and its freedom from irritating elements. Detailed study of two surgical patients and routine ward observations on six others confirmed clinically our experimental observations on animals. At no time was there a permanent weight loss, and an increase was observed frequently. Nausea and vomiting occurred a number of times in association with jejunal feeding, but invariably they were traced to an excessive rate of administration, and disappeared with its adjustment. A maximum drip rate as high as 300 c.c. per hour was attained clinically, which appeared to be near the limit of tolerance for these patients, but a rate of about one-half of this is sufficient when administration is more or less continuous. However, immediately after operation, jejunal alimentation should be started at a low rate, preferably around 60 c.c. per hour. The speed with which this can be increased depends on the reactions of the individual patient, but after a five-day period of adaptation, a rate of 150 c.c. per hour may be attained. To introduce 2,400 Cal. under these conditions, not more than sixteen hours are required. This rate of administration presumes that no physiologic saline solution is added to the nutrient material. When such addition is necessary, especially during the first few days postoperatively, it is generally made by substituting the salt solution for an equal volume of the aliment. Diarrhea in association with jejunal feeding was encountered in only one of the eight patients, and cramps in two of them, but there was good reason to believe that these disturbances were unrelated to the predigested aliment.

It must be recognized that the disturbing symptoms which may result from inadequacies in composition of the aliment, or in the conditions of its administration, may occur also as a result of other factors specifically associated with the patient's condition. Nausea, vomiting, abdominal pain, and cramps complicate practically every major abdominal operation during the first five days postoperatively. These may occur even after the ingestion of tea or other fluids. It is difficult, therefore, to evaluate properly the role of the jejunal aliment itself in the occasional causation of these symptoms. Nevertheless, there is ample evidence that the synthetic predigested mixture employed in these studies does not induce these gastrointestinal disturbances if it be properly administered. The value of any enteric feeding mixture depends also upon the efficiency of its absorption and utilization by the body. The adequacy of this new aliment in this regard also has been demonstrated both experimentally and clinically by the maintenance or gain of body weight in all instances in which it was used. The evidence from this preliminary investigation, therefore, has justified the routine clinical use of this new enteric aliment.

SUMMARY

The clinical uses of jejunal alimentation are briefly reviewed. Reasons for the current lack of widespread use of this feeding procedure are analyzed, in relation to the physiologic factors concerning the composition of the nutrient material. On the basis of these factors, the formula for a synthetic predigested aliment is presented, together with the method of its preparation. In contrast with previous formulas, emphasis is laid upon the incorporation of predigested proteins, the marked reduction in the fat content, the use of partially predigested carbohy-

drate free of hexose sugars, and the liberal supply of essential salts and vitamins. Evidence for the efficacy of this nutrient mixture is based on increase in body weight and absence of cramps and diarrhea, specifically associated with its administration to experimental animals and patients with jejunostomy. Furthermore, it has been shown that the occasional occurrence of untoward symptoms like nausea, vomiting, and distention can be eliminated by starting the rate of feeding at 60 c.c. per hour and gradually increasing it to a maximum of 150 to 200 c.c. per hour about the fifth postoperative day, the speed of increase and the upper limit being established for each patient individually. The importance of sterilization of the aliment and the drip apparatus is also discussed. This preliminary investigation, therefore, has justified the clinical use of this synthetic predigested aliment, and the response of a larger group of cases to its administration is now being studied.

REFERENCES

1. Benedict, F. G.: *Vital Energetics: A Study in Comparative Basal Metabolism*, No. 503, Washington, D. C., 1938, Carnegie Institution of Washington.
2. Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*, ed. 3, Baltimore, 1943, Williams & Wilkins Company.
3. Bockus, H. L.: *J. A. M. A.* 82: 351, 1924.
4. Brunschwig, A., Clark, D. E., and Corbin, N.: *Ann. Surg.* 115: 1091, 1942.
5. Busch, W.: *Virchows Arch.* 14: 140, 1858.
6. Colp, R., and Druckerman, L. J.: *Ann. Surg.* 117: 387, 1943.
7. Cornell, A., and Hollander, F.: *Rev. Gastroenterol.* 9: 354, 1942.
8. Cowgill, G. R.: *J. Biol. Chem.* 56: 725, 1923.
9. Einhorn, M.: *Med. Rec.* 78: 92, 1910.
10. Elman, R., and Weiner, D. O.: *J. A. M. A.* 112: 796, 1939.
11. Elman, R., Weiner, D. O., and Bradley, E.: *Ann. Surg.* 115: 1160, 1942.
12. Elman, R., and Lischer, C.: *Internat. Abstr. Surg.* 76: 503, 1943.
13. Henning, N.: *Arch. f. Verdauungskr.* 41: 321, 1927.
14. Kirschner, M.: *Arch. f. klin. Chir.* 157: 561, 1929.
15. Mann, F. X., and Bollman, J. L.: *Ann. Surg.* 93: 794, 1931.
16. McGee, C., and Emery, Jr., E. S.: *Proc. Soc. Exper. Biol. & Med.* 45: 475, 1940.
17. Mensing, E. H.: *Wisconsin M. J.* 32: 168, 1933.
18. Mensing, E. H., and Kelley, E. H.: *Am. J. Surg.* 20: 99, 1933.
19. Mulholland, J. H., Co Tui, Wright, A. M., and Vinci, V. J.: *Ann. Surg.* 117: 512, 1943.
20. Rosenak, S., and Hollander, F.: *Clinics* 1: 638, 1944.
21. Scott, H. G., and Ivy, A. C.: *Ann. Surg.* 93: 1197, 1931.
22. Scott, H. G., Holinger, P. H., and Ivy, A. C.: *Proc. Soc. Exper. Biol. & Med.* 28: 569, 1931.
23. Sherman, H. C.: *Chemistry of Food and Nutrition*, Ed. 6, New York, 1941, The Macmillan Company.
24. Stewart, J. D.: *Ann. Surg.* 96: 225, 1932.
25. Surmay: *Bull. gén. de therap.* 94: 445, 1878; *Ibid.* 95: 198, 1878.
26. Walters, W., and Hartman, H. R.: *Arch. Surg.* 40: 1063, 1940.
27. Wangenstein, O. H.: *Intestinal Obstructions*, ed. 2, Springfield, Ill., 1942, Charles C Thomas.
28. Wolfer, J. A.: *Ann. Surg.* 101: 708, 1935.

Editorial

Peptic Ulcer

A SYMPOSIUM on peptic ulcer is always timely, because ulcers of the stomach and duodenum are so frequently encountered and because of the likelihood of their recurrence. Generally, it is important to differentiate between an ulcer of the duodenum and one of the stomach, because it is quite universally accepted that the former is primarily a medical problem, whereas the latter is largely a surgical one. The reason for the differentiation between the two types is the susceptibility of the gastric mucosa to malignant change and the possibility either of a benign ulcer's becoming malignant or of the ulcer's masking an underlying malignant change.

There are many factors which are responsible for the development of peptic ulceration, one of the most important of which is a constitutional predisposition which is inherent in the individual and which he possesses for his entire life. For this reason, it is imperative in the handling of an ulcer patient to have him change his mode of living for the rest of his life in such a way that the precipitating factors responsible for the production of an ulcer are obviated. Of the precipitating factors, unquestionably hyperacidity is the most important. This is substantiated by the fact that the various methods of therapy which are employed, with few exceptions, either prevent or control gastric acidity. Although the healing of an uncomplicated peptic ulcer usually offers no difficulty, unfortunately too few physicians appreciate the importance of the prevention of its recurrence, which is possible only with a rational understanding by the patient that he must avoid those factors which produce increased acidity. Whereas the detrimental effects of alcohol and tobacco have been known for some time, the importance of refraining from the use of these substances after the ulcer has healed is not sufficiently realized by the medical profession generally. The detrimental effect of caffeine to patients who have an ulcer diathesis has not been emphasized until relatively recently. The investigations of Ivy and his associates and of Merendino and his associates clearly indicate the necessity of abstaining from the use of caffeine-containing drinks by the ulcer patient. The psychic factor in the production of ulcer is a prominent one. Although more difficult to define than the role which gastric acidity may play, it is a well-known fact that a patient with an ulcer is frequently relieved of all of his symptoms the moment he goes on a vacation even though he may disregard his dietary regimen entirely.

In the treatment of an active ulcer, antacids as well as frequent feedings, both of which tend to neutralize the acidity, are of value. Of importance also is the use of antispasmodics in order to favor the reflux of the alkaline duodenal secretion into the stomach by overcoming pylorospasm. Frequently the use of continuous drip is essential in the control of the ulcer as emphasized by the results of Winkelstein and his associates.

As emphasized here, treatment of the acute ulcer is not difficult. Generally, and usually within a few weeks, the ulcer will heal completely. Too frequently, however, the physician is likely to discharge his patient without emphasizing to him the necessity of his avoiding those factors which cause hyperacidity and which will result in the recurrence of the ulcer. In outlining such a therapy, it is not necessary to have the patient lead the life of an invalid. As a matter of fact, simply by eating frequently, by avoiding overeating at any time for the rest of his life, and by avoiding smoking and drinking and the use of condiments, he will be able to remain comfortable without exacerbations of the ulcer.

The surgical treatment of ulcer of the duodenum is largely that of complications, there being a few cases of intractability of the ulcer which will not respond to medical therapy in which a surgical procedure is justified and which is necessary to bring about relief. It is the consensus at the present time that when surgery is indicated in the treatment of peptic ulcer, a radical procedure is necessary. Gastrojejunostomy should be done seldom in the treatment of peptic ulcer and is indicated only in the case in which, because of a long-standing cicatricial stenosis of the duodenum or the pylorus, there has resulted an atrophic gastritis with its concomitant hypochlorhydria and achlorhydria. The danger of the development of a jejunal ulcer in a patient with a hyperacidity is far too great to justify a gastrojejunostomy in such a case. Although there is some difference of opinion concerning the amount of stomach that should be removed in doing a partial or subtotal gastrectomy for peptic ulcer, there is general agreement that all of the pylorus and the pyloric antrum must be removed. As repeatedly emphasized by Wangensteen and demonstrated conclusively by the work of Lannin, massive resections are essential, and it is also important that as short an intestinal loop be used to make the anastomosis as possible in order to insure against the recurrence of an ulcer.

In gastric ulcer, one should always suspect the possibility of malignant change or the coexistence of a neoplasm with ulceration. For this reason, a gastric ulcer which does not heal completely within a short period of time should be resected, because the best time to treat gastric carcinoma is at the time when the diagnosis cannot be made.

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Announcement

In compliance with the directives imposed by the War Production Board limiting the amount of paper consumed in the production of this JOURNAL, the publishers find it necessary to change the format. As soon as these restrictions are lifted the original format will be restored. Even though the number of pages has been reduced, the actual content of the journal has not been decreased to any appreciable extent.

proximate number of coliform organisms per gram of feces. Before sulfasuxidine is administered, the colonies of coliform organisms on the plate will be too numerous to count. When the plate count has dropped to 100, the feces being studied will contain roughly 10,000 coliform organisms per gram. On practice has been to consider a coliform population not exceeding 1,000 organisms per gram of feces as indicating a satisfactory preoperative preparation of the colon, and the corresponding count on the streaked plate should not exceed twenty colonies.

When the coliform count has dropped to 1,000 organisms per gram of feces the stools will have become semifluid, relatively odorless, small in bulk, and mucoid.

In 1943, Poth and Ross^{21, 22} published their results on a continued study of the acylated sulfonamides and presented data on phthalylsulfathiazole (Sulfathalidine) which showed this compound to possess approximately twice the bacteriostatic activity shown by sulfasuxidine as indicated by their antibacterial actions against the coliform organisms in the gastrointestinal tract of dog and man.²³ These findings were confirmed and extended by Mattis, Benson, and Koelle.²⁴

In general the effects of sulfasuxidine and sulfathalidine are similar, as indicated by their antibacterial action against the coliform organisms. Sulfathalidine does not tend to reduce the feces to a semifluid state, nor does it effect as great a degree of change in the odor of the stools. Obviously, the action of the drugs does differ somewhat, both qualitatively and quantitatively. Sulfathalidine has the greater tendency to alter the coliform count and will lower the count even in the presence of severe diarrhea. With the administration of this latter drug, however, the feces tend to become tenacious and stringy and result in less efficient mechanical emptying of the bowel and a less satisfactory surgical preparation unless enemas and purgatives are used simultaneously.

Dosage.—Since sulfathalidine has twice the bacteriostatic activity of sulfasuxidine, one-half the amount of the former drug would have a bacteriostatic action, as indicated by the effect on the coliform organisms, equal to that of the latter compound. The usual dosage of sulfasuxidine is 0.02 Gm. per pound of body weight every four hours, or 3.0 Gm. every four hours for an average-sized man (150 pounds). This dosage is approximately 0.25 Gm. per kilogram each twenty-four hours. The corresponding dose of sulfathalidine is 1.5 Gm. every four hours. In the case of these drugs, which are sparingly absorbed and whose effective action is limited locally to the gastrointestinal tract, it is not the weight of the patient but rather the inner surface area of bowel, and the rate at which the drug passes over this surface, which determines the quantity of drug required to effect the desired antibacterial action. In the presence of an extensive diarrhea, the dosage must be doubled to effect an equivalent alteration of the bacterial flora. It has been found that sulfathalidine is the drug of choice when diarrhea is present or whenever enemas and purgatives are used.

Toxicity.—Of the several thousand individuals who have received these drugs in full therapeutic doses, there has been but a single fatality reportedly due to drug intoxication following the administration of sulfasuxidine. In this instance^{25, 26} a patient, previously shown to be sensitive to sulfathiazole, developed a fatal acute agranulocytosis following the administration of 159 Gm. of succinylsulfathiazole in the course of twelve days. Fever therapy, in the form of the injection of killed typhoid organisms was being administered simultaneously.

Clay and Pickrell²⁷ reported two reactions following succinylsulfathiazole administration. One of these consisted of a hematuria which had not been previously reported. An unusually high blood level of 3.8 mg. per cent of sulfathiazole was found two days after the drug was discontinued. No sulfasuxidine determinations were reported. In my experience it has not been unusual to find sulfathiazole being given when sulfasuxidine had been ordered; and unless this possibility was eliminated, such an occurrence might explain this isolated observation. Hematuria usually means crystalluria, which will not occur when sulfasuxidine is administered unless the urine has an unusually strong acid reaction.

I have observed two instances in which patients developed myalgia, arthralgia, hyperpyrexia, and a rash following the administration of sulfasuxidine. These reactions were sufficiently severe to contraindicate continued drug therapy. Mild reactions to both sulfasuxidine and sulfathalidine are not infrequent, and an occasional severe reaction must be expected. Ordinarily, these reactions consist of nothing more severe than headache, malaise, anorexia, and moderate rise of temperature and do not require that the therapy be interrupted. Of the two drugs, sulfathalidine is the least toxic. Barger²⁸ found, from a study of over 2,000 patients to whom sulfasuxidine was administered, that toxic reactions of sufficient degree to indicate discontinuance of the therapy occurred in less than 1 per cent of the cases. Sulfathalidine was then administered to these patients sensitive to sulfasuxidine without the recurrence of toxic manifestations in a single instance. Obviously, a severe reaction may occur and any patient receiving either of these drugs should be under adequate observation.²⁹

Allen³⁰ reported that approximately one-fifth of his patients having carcinoma of colon showed increased hemorrhage after receiving sulfasuxidine for four or five days. I have noticed an increase of bleeding in an occasional patient, but the incidence has not been so high. In my experience the increased bleeding has not been sufficiently serious to force an emergency operation or a change in the preoperative management. An increased tendency to bleed at the line of suture has not been observed during the postoperative period when sulfasuxidine was administered.

THE PREOPERATIVE PREPARATION OF THE COLON

Not only is it desirable to lower the bacterial count and simplify the flora of the bowel before operation, but the colon must be mechanically clean and empty. Ordinarily these conditions can be accomplished by merely placing the patient on a low residue diet and administering succinylsulfathiazole. Occasionally it may be necessary to use more vigorous methods to clear the bowel of fecal material, and most surgeons insist upon using purgatives and enemas as a part of the surgical preparation. In this event, and in the absence of obstruction, the patient is placed on a residue-free diet high in protein and carbohydrate, a saline purgative is given to effect efficient evacuation of the bowel by several watery stools, after which a high colonic flush is administered. The diet should consist of strained fruit juices fortified with lactose, gelatin, casein, jello, and vitamin concentrates. A minimum of 100 Gm. of protein should be taken daily, especially if the patient has been on a restricted protein intake. The patient will take this diet readily, especially if the simple carbonated drinks are given. Alcoholic beverages in moderate quantities may be allowed when the patient is accustomed to taking them and they are well tolerated.

Occasionally a malnourished patient will not respond to an adequate protein intake. Only the simplest emergency operations should be done when the plasma protein concentration is less than 5.5 per cent and the A-G ratio is less than 1.5. Starved patients frequently have fatty livers (Wangensteen²¹) and tolerate anesthesia and extensive operative procedures poorly. It is not unusual to find that a patient with protein deficiency will refuse to eat and may require intravenous amino acids. After three to four days administration of amino acids intravenously with parenteral vitamins, the appetite will return and adequate food will be taken by mouth and be utilized to replace the depleted protein stores.

A. The Use of Sulfasuxidine for Preoperative Preparation.—Sulfasuxidine, 3.0 Gm., is given orally every four hours for at least seven days if no observations are made on the coliform content of the feces. Quantitative bacteriologic studies of the feces of 350 patients show less than 1,000 coliform organisms per gram of wet feces after the following periods of treatment: (1) 37 per cent within three days of therapy, (2) 80 per cent within five days of therapy, and (3) 94 per cent within seven days of therapy. If the coliform count is followed by the streak technique, the drug is given until the number of coliform colonies on the streaked plate is less than twenty. In the presence of a watery diarrhea, 3.0 Gm. of sulfathalidine each four hours should be substituted for the sulfasuxidine. Should the diarrhea stop, the dosage should be reduced to 1.5 Gm. of sulfathalidine. If an enema is given on the evening preceding operation, it should consist of sterile tap water containing 10.0 Gm. of sodium bicarbonate and 6.0 Gm. of sulfasuxidine powder to the liter administered as a high colonic flush in sufficient quantity to ensure complete evacuation of the colon. I have seldom found this measure necessary to secure an empty, collapsed bowel at the time of operation. Sulfasuxidine appears to be slightly irritating to the mucous membrane of the large bowel resulting in an increased secretion of mucous characteristically accompanied by three or four small soft bowel movements daily.

*B. The Use of Sulfathalidine for Preoperative Preparation.*²—Sulfathalidine, 1.5 Gm., is given orally every four hours for at least seven days if no observations are made on the coliform content of the feces. Again, if the coliform count is observed using the simplified streak technique, the therapy is continued until the number of coliform colonies on the streaked plate is less than twenty. This observation will frequently allow a considerable reduction in the time required for satisfactory preparation, because many patients will have shown a significant alteration of the bacterial flora within three days of therapy.

Sulfathalidine is not as efficient as sulfasuxidine in effecting mechanical cleansing of the bowel, because it does not render the feces as fluid. Mild purgation must ordinarily be used in conjunction with the administration of phthalylsulfathiazole. The patient should have at least one bowel movement daily. Observation of the size, consistency, and odor of these stools will readily indicate when the colon is satisfactorily evacuated. Should the patient develop a watery diarrhea, the dosage of sulfathalidine should be doubled. If enemas are used, they should consist of sterile, warm, tap water containing 10.0 Gm. of sodium bicarbonate and a suspension of 6.0 Gm. of sulfathalidine powder to the liter.

It must be remembered that the sulfonamides are bacteriostatic substances and that they do not ordinarily possess bacteriocidal properties. It is required,

therefore, that these drugs come in contact with the entire mucosal surface to effect a significant alteration of the bacterial flora. A segment of bowel into which no drug passes will continue to feed organisms into distal portions of bowel, and the feces will continue to show high bacterial counts. The time required to alter the bacterial flora in the presence of diverticulosis is prolonged. In the presence of fecal fistulas diverting the fecal stream away from the distal portion of bowel, not only must the usual dose of drug be given by mouth, but an equal quantity of drug must be introduced into the distal segment of bowel if the flora in this portion is to be affected.

It is not universally agreed that sulfasuxidine is the drug of choice for the preoperative preparation of the colon, and it certainly would not be so if a watery diarrhea exists or if enemas and purgatives are administered. Whichever drug (sulfasuxidine or sulfathalidine) is superior will be determined by the entire preoperative management and must be fitted into the routine of the individual physician. Sulfathalidine will likely be preferred by many surgeons, because its greater antibacterial activity will permit the use of purgatives and enemas. I have rigorously avoided the use of any procedures accessory to the administration of either succinylsulfathiazole or phthalylsulfathiazole. Under these conditions I consider succinylsulfathiazole to be superior. Bargen,^{19, 28} on the basis of experience gained from the observation of 2,075 patients treated with sulfasuxidine and sulfathalidine in 1943 and 1944, states: "Succinylsulfathiazole (sulfasuxidine), so far, has proved to be the drug of choice in preoperative management, with phthalylsulfathiazole (sulfathalidine) serving as an alternative when toxicity to succinylsulfathiazole manifests itself." It is unnecessary, routinely, to determine the level of these drugs in the blood, because only about 5 per cent of the ingested drug is absorbed and the rate of excretion by the kidneys is rapid. In the event of an untoward reaction the blood level should be determined.

THE POSTOPERATIVE ADMINISTRATION

There may be little indication for the postoperative administration of these locally active sulfonamides; for example, when the operative procedure ends in a colostomy as in the case of an abdominal-perineal resection. When bowel suture is performed, however, and the involved segment is retained in the peritoneal cavity, the bacterial flora should be controlled for twelve days postoperatively so as to pass the period during which leakage may occur at the suture line. During the first twenty-four hour postoperative period continuous gastric suction is used, because this period includes recovery from the anesthetic when air is frequently swallowed in considerable quantities. Ordinarily, the patient can then tolerate water of room temperature in 30 c.c. quantities at hourly intervals and 1.5 Gm. of phthalylsulfathiazole every four hours. It is best to give a single 0.5 Gm. tablet of drug on three occasions during the four-hour interval rather than the entire drug in a single dose. The drug is tolerated surprisingly well. During the postoperative period, sulfathalidine is the drug of choice.

SUPPLEMENTARY DRUG THERAPY

As stated by Pemberton and associates²⁰: "In spite of the availability of the newer chemotherapeutic agents, the chief cause of hospital deaths after operation on the large intestine continues to be infection. Of the thirty-four hospital deaths after operations on the large intestine in 1943, seventeen were caused by peritonitis, three were primarily due to pneumonia and one was from

septicemia." In this series the operative mortality due to peritonitis is only 1.0 per cent, but it does represent the greatest single cause of hospital death following operations on the colon. The two adjuvants used consisted of the preoperative preparation with succinylsulfathiazole and the intraperitoneal instillation of sulfathiazole powder at the time of operation. It has been demonstrated repeatedly that the instillation of sulfathiazole intraperitoneally is of value in preventing peritonitis.^{17, 32} In the event there is wound sepsis about a fecal fistula, Keene¹⁸ recommended that sulfathiazole or sulfadiazine should be given for forty-eight hours before operation, and so long as is deemed necessary postoperatively, in full therapeutic doses to give optimum tissue saturation.

As penicillin becomes more readily available, it will, no doubt, figure as an additional adjuvant.

DISCUSSION

The aim of this paper is to delineate the relative values of sulfasuxidine and sulfathalidine as agents in preparing the colon for operation: not only to reduce and simplify the bacterial population and thereby reduce postoperative infection of the peritoneal cavity and abdominal wall, but also to place the colon in the best mechanical condition by removal of fecal material and reduction of postoperative distention.

It has been demonstrated repeatedly that these acylated sulfonamides alter and simplify the bacterial flora of the gastrointestinal tract. The question is raised as to whether such a modification is of any practical value in making surgery of the large bowel a safer procedure.

The first report on a series of fifty patients receiving succinylsulfathiazole both preoperatively and postoperatively when operations were performed on the colon was by Poth⁷ in 1942. No fecal fistulas developed, there were no instances of peritonitis, and there were no deaths.

In 1943, Allen¹¹ expressed the opinion that with the use of sulfasuxidine there was a definite tendency to increase the number of single-stage operations on the large bowel. By 1945, this author³⁰ considers sulfathalidine the drug of choice for the preoperative management of patients with carcinomas of the colon, because this drug shows no tendency to cause increased hemorrhage from ulcerating lesions. In addition sulfadiazine is given intravenously beginning on the morning of the operation. Sulfathalidine is administered postoperatively as soon as tolerated. This procedure has permitted open anastomoses, deep in the pelvis, without instituting drainage to the area.

Also in 1943, Zintel, Lockwood, and Snyder¹³ and Archer¹⁴ reported favorably on the use of succinylsulfathiazole in the preoperative management of colon resections.

Behrend¹⁵ (1944) was most enthusiastic about the value of sulfasuxidine which has permitted him to substitute primary anastomoses without an accompanying cecostomy or other form of enterostomy for the Mikulicz operation in surgery of the colon.

Archer and Lehman¹⁶ have stressed the importance of an adequate protein intake during the period of preoperative preparation. They also used succinylsulfathiazole. They reported thirty-six successive operations performed on the colon with one death attributable to the failure of the drug to protect a 71-year-old man from a localized peritonitis, pneumonia, and lung abscess.

Dixon and Benson¹⁷ in 1944, compared the results obtained on the surgical closure of the stomata in 274 Mikulicz operations using four different proce-

dures: Group I, 102 patients received no sulfonamides; Group II, 40 patients received sulfanilamide locally; Group III, 30 patients received sulfathiazole locally; and Group IV, 102 patients received succinylsulfathiazole orally for three days preoperatively (none in the distal segment) and sulfathiazole locally.

TABLE 1. COMPARATIVE MORBIDITY FOLLOWING CLOSURE OF COLONIC STOMATA AS INFLUENCED BY SULFONAMIDE THERAPY

GROUP	IMMEDIATE OPERATIVE RESULTS (IN PER CENT)		
	WOUND INFECTION	FECAL DRAINAGE	HEALED IN 14 DAYS
I	84	30	8
II	77	25	10
III	63	17	20
IV	13	2	80

Table I shows the occurrence of wound infection in 84 per cent of cases in which no sulfonamides were used as compared to 80 per cent healed wounds by the fourteenth postoperative day after preoperative administration of succinylsulfathiazole and local implantation of sulfathiazole. The use of sulfanilamide and sulfathiazole locally gave but slightly better results than the untreated controls.

Keene^{18, 33} has prepared some fifty patients with war injuries to the colon by the administration of sulfasuxidine for eight days. The proximal and distal segments of bowel are irrigated with 1:4000 potassium permanganate on the morning of the operation; 4 Gm. of sulfanilamide were placed in the peritoneal cavity and 2 Gm. in the abdominal wound, and the skin left open for forty-eight hours. Primary union of bowel occurred in 100 per cent of the cases.

One should always emphasize that sulfasuxidine and sulfathalidine are properly used only as aids in colonic surgery and should not in the slightest degree encourage a breakdown in proved surgical principles. So-called aseptic procedures should be used whenever possible, but, when necessary, an open anastomosis can be done with a much greater degree of safety. With the proper alteration of the bacterial flora, the preservation of blood supply by the avoidance of tension and the proper placement of fine sutures becomes much more important than chance soiling of tissues by the modified contents of the bowel.

CONCLUSIONS

The evidence which has accumulated over the past four years indicates that succinylsulfathiazole and phthalylsulfathiazole, when given in adequate doses, are bacteriostatic agents which will produce a significant modification of the bacterial flora of the bowel and that their proper administration will help to give a satisfactory mechanical preparation of the bowel preceding surgical operations while the patient is maintained on an adequate protein and carbohydrate diet. The postoperative morbidity studies indicate that these drugs, when properly used in the preoperative and postoperative surgical periods, will act as aids, contribute to a lowering of the operative mortality, and make an occasional procedure possible which might otherwise not be feasible.

REFERENCES

1. Poth, E. J., and Knotts, F. L.: Succinyl Sulfathiazole, a New Bacteriostatic Agent Locally Active in the Gastrointestinal Tract, *Proc. Soc. Exper. Biol. & Med.* 48: 129, 1941.
2. Poth, E. J., Knotts, F. L., Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: I. Succinylsulfathiazole, a New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract. *Arch. Surg.* 44: 187, 1942.

3. Welch, A. D., Mattis, P. A., and Latven, A. R.: A Toxicological Study of Succinylsulfathiazole, *J. Pharmacol. & Exper. Therap.* 75: 231, 1942.
4. Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, *Arch. Surg.* 44: 208, 1942.
5. Sarnoff, S., and Poth, E. J.: Intestinal Obstruction; I. The Protective Action of Succinylsulfathiazole Following Simple Venous Occlusion, *SURGERY* 16: 927, 1944.
6. Bloomfield, A. L., and Lew, W.: Prevention by Succinyl Sulfathiazole of Ulcerative Cecitis in Rats, *Proc. Soc. Exper. Biol. & Med.* 51: 28-29, 1942.
7. Poth, E. J.: Succinylsulfathiazole; An Adjuvant in Surgery of the Large Bowel, *J. A. M. A.* 120: 265, 1942.
8. Poth, E. J., Chenoweth, B. M., and Knotts, F. L.: A Preliminary Report on the Treatment of Bacillary Dysentery With Succinylsulfathiazole, *J. Lab. & Clin. Med.* 28: 162, 1942.
9. Firor, W. M.: Intestinal Antisepsis With Sulfonamides, *Ann. Surg.* 115: 829, 1942.
10. Poth, E. J.: The Use of Succinylsulfathiazole and Phthalylsulfathiazole as Intestinal Antiseptics, *Texas State J. Med.* 39: 369, 1943.
11. Allen, A. W.: Carcinoma of the Colon, *SURGERY* 14: 350, 1943.
12. Hardy, A. V., Burns, W., and De Capito, T.: Cultural Observations on the Relative Efficacy of Sulfonamides in Shigella Dysenteriae Infections, *Pub. Health Rep.* 58: 689, 1943.
13. Zintel, H., Lockwood, J. S., and Snyder, J.: Bacteriological Considerations in Sulfonamide Prophylaxis Against Peritonitis, *Bull. Am. Coll. Surgeons* 28: 51, 1943.
14. Archer, H. L.: Preparation for Colonic Surgery With Succinyl Sulfathiazole and Dietary Modifications, *Bull. Am. Coll. Surgeons* 28: 51, 1943.
15. Behrend, M.: Succinylsulfathiazole (Sulfasuxidine) and the Elimination of the Mikulicz Operation, *S. Clin. North America* 24: 238, 1944.
16. Archer, H. L., and Lehman, E. P.: Clinical and Laboratory Experience With Succinylsulfathiazole, *Ann. Surg.* 119: 518-525, 1944.
17. Dixon, C. F., and Benson, R. E.: Closure of Colonic Stoma: Improved Results With Combined Succinylsulfathiazole and Sulfathiazole Therapy, *Ann. Surg.* 120: 562-571, 1944.
18. Keene, C. H.: Reconstruction of Wounds of the Colon, *Surg., Gynec. & Obst.* 79: 544-551, 1944.
19. Barga, J. A.: Annual Report on Intestinal Diseases for 1943, *Proc. Staff Meet., Mayo Clin.* 19: 602-605, 1944.
20. Pemberton, J. deJ., Dixon, C. F., Waugh, J. M., and Black, B. M.: Annual Report of Surgery of the Large Intestine for 1943, *Proc. Staff Meet., Mayo Clin.* 19: 605-612, 1944.
21. Poth, E. J., and Ross, C. A.: Phthalylsulfathiazole, a New Bacteriostatic Agent, *Federation Proc.* 2: 89, 1943.
22. Poth, E. J., and Ross, C. A.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives; II. Phthalylsulfathiazole, A New Chemotherapeutic Agent Locally Active in the Gastrointestinal Tract, *Texas Rep. Biol. & Med.* 1: 345-370, 1943.
23. Poth, E. J., and Ross, C. A.: The Clinical Use of Phthalylsulfathiazole, *J. Lab. and Clin. Med.* 29: 785-808, 1944.
24. Mattis, P. A., Benson, W. M., and Koelle, E. S.: Toxicological Studies of Phthalylsulfathiazole, *J. Pharmacol. & Exper. Therap.* 81: 116, 1944.
25. Johnson, S. A. M.: Acute Agranulocytosis Due to Administration of Succinylsulfathiazole, *J. A. M. A.* 122: 668, 1943.
26. Poth, E. J., and Johnson, S. A. M.: Correspondence in Regard to Granulocytopenia After Use of Succinylsulfathiazole, *J. A. M. A.* 123: 112, 1943.
27. Clay, R. C., and Pickrell, K. L.: Toxic Reactions to Succinylsulfathiazole, *J. A. M. A.* 123: 203-204, 1943.
28. Barga, J. A.: Personal Communication.
29. Crohn, B. B.: The Clinical Use of Succinyl Sulfathiazole (Sulfasuxidine), *Gastroenterology* 1: 140, 1943.
30. Allen, A. W.: Personal Communication.
31. Wangenstein, O. H.: Primary Resection (Closed Anastomosis) of the Colon and Rectosigmoid, *SURGERY* 14: 403, 1943.
32. Poth, E. J., and Fernandez, E. B.: Experimental Studies of the Value of Sulfathiazole in Peritonitis, *SURGERY* 13: 847-858, 1943.
33. Keene, C. H.: Personal Communication.

ELECTIVE OCCLUSION AND EXCISION OF THE PORTAL VEIN

AN EXPERIMENTAL STUDY*

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A PATIENT was subjected to laparotomy for excision of a carcinoma of the neck of the pancreas. The posterior aspect of the tumor had infiltrated the first portion of the portal vein but this was not appreciated until the vein was accidentally opened. Copious hemorrhage ensued and when finally controlled, the clamped and transected portal vein was separated from the clamped and transected superior mesenteric vein by about 4 cm. distance. Attempts to approximate these vessels for anastomosis failed, as the tension was too great and the vessel walls tore easily. The portal and superior mesenteric veins were ligated. A pancreatoduodenectomy was performed. The patient's condition was not satisfactory and the procedure rapidly terminated by gastrojejunostomy and insertion of a catheter into the transected common duct and its ligation in place; the abdominal wound was closed with the catheter brought out through it. The pancreatoduodenectomy was not properly completed because it was felt that the patient would succumb in a few hours as a result of the portal ligation. Instead, her condition improved after operation and for several days it appeared as though she might survive. On the eighth postoperative day clinical signs of peritonitis developed and she died on the tenth postoperative day. Necropsy revealed bile peritonitis that resulted from leakage about the catheter in the common duct. There was no evidence of vascular disturbances due to portal vein transection. There were venous anastomoses at the root of the mesentery between mesenteric veins and radicals entering the inferior vena cava; there were also anastomoses between portal and caval circulations in the spaces of Retzius. Twenty years previously there had been a pelvic operation through a low midline incision and the greater omentum was extensively adherent to the lower anterior abdominal wall; the adhesions were very vascular. This was also an anastomosis between portal and caval venous systems. (Details previously published [Brunschwig]).

There are not a few instances on record of occluding thrombosis of the portal vein which was gradual enough to permit of the development of collateral anastomoses and under which conditions continued existence was possible.

These facts raised the question of devising a technique for gradual occlusion of the portal vein that would permit of the development of collateral circulation in relatively short time so that excision of the portal and terminal segments of superior mesenteric vein might be carried out with survival.

A review of the literature reveals that Oré, in 1856, was the first to demonstrate the feasibility of gradual occlusion of the portal vein in dogs. This work was carried out before the advent of asepsis. The abdomen was opened through an oblique incision parallel to the right costal margin, the portal vein isolated,

This paper was to have been presented at the meeting of the Society of University Surgeons, New York, N. Y., Feb. 8, 1945. (Meeting canceled.)

*This study was facilitated by the Charles and Mary F. S. Worcester Memorial Fund for Cancer Research, The University of Chicago.

a thread passed beneath it, the wound closed, and the two long ends of the thread tied over the animal's back. On the fourth day, one thread was cut and the remaining one pulled out. The inflammatory reaction induced by the presence of the thread about the portal vein induced a gradual thrombosis in the latter which was not too sudden or complete to cause death. Two animals survived for periods sufficiently long (eleven and twenty days) to demonstrate that the collateral venous anastomoses had developed.

Solowieff, in 1875, demonstrated that if preliminary ligations of the superior mesenteric, then gastrosplenic vein, were carried out at five- to six-day intervals, the portal vein could be ligated with survival of the animal. Oré's observations were confirmed by Bernard in his published lectures on diabetes in 1877. Tilmann, in 1899, demonstrated that if the portal vein is stenosed to one-half its diameter by a ligature, at a second operation eight days later the vein could be completely occluded with survival. Ito and Omi, in 1902, carried out some thirty experiments on stage ligation and also preliminary ligations of large tributaries to the portal vein prior to its complete occlusion. In some instances omentopexy was also performed but the significance of this was questioned. Neuhof, in 1913, reported experiments in dogs in which the portal was gradually occluded during three-stage ligature compressions over a period of fourteen days. He also demonstrated that preliminary ligation of large tributaries would finally permit of total occlusion of the portal vein with survival. There appears to have been no further reports of such experiments until 1931, when Dragstedt again reported successful occlusion of the portal in various species of animals by a two-stage procedure.

It has long been known that dogs survive primary complete portal ligation for only one-half to two and one-half hours. Elman and Cole pointed out, in 1934, that the clinical picture was that of progressive and profound shock because of the accumulation of blood in the occluded portal venous system with resulting marked reduction in circulating blood volume.

EXPERIMENTAL

A. Omentopexy in the dog does not afford sufficient collateral venous anastomoses to permit of survival after subsequent complete portal ligation. In four dogs, laparotomy was performed through a midline incision, splenectomy was performed, anterior parietal peritoneum was incised on each side, and large masses of omentum were tucked through these openings into the abdominal wall and apposed to the musculature by interrupted sutures. The abdomen was then closed. Twenty to thirty-four days later laparotomy was again performed and the portal vein ligated. Survivals varied from one to two and one-half hours. Necropsies revealed severe venous congestion in the portal system and marked cyanosis of the bowels. The omental adhesions to the abdominal wall were predominantly fibrous with little vascularity. This is in contrast to man, where such omental adhesions are usually quite vascular. The results are summarized in Table I.

TABLE I. OMENTOPEXY, THEN LIGATION, OF PORTAL VEIN

DOG	TIME AFTER OMENTOPEXY PORTAL VEIN LIGATED	SURVIVAL AFTER PORTAL VEIN LIGATION
823	20 days	2+ hours
855	30 days	1½ hours
856	31 days	2½ hours
832	2 operations, the second more extensive, performed 3 weeks after first; portal ligation 13 days later	1 hour 10 minutes

B. The portal vein may be successfully divided and occluded by a "transection ligature" (Table II). Dogs were subjected to laparotomy, a linen thread passed about the portal vein proximal to entrance of the gastrosplenic vein, the long ends brought out of the wound and tied over the back. On the fourth postoperative day the threads were pulled upon for a brief period. This was repeated each day subsequently. On the eighth to twelfth day post-operatively the intact loop was pulled out, thus indicating that it passed through the portal. Division of the vessel with occlusion of it did not always obtain. In some cases the lumen persisted (or reformed) but there was stenosis at the transection site (Fig. 1). A period of about ten days (with some variation) seems to be adequate for the development of venous collateral circulation to permit of survival with occluded portal vein (Fig. 2).

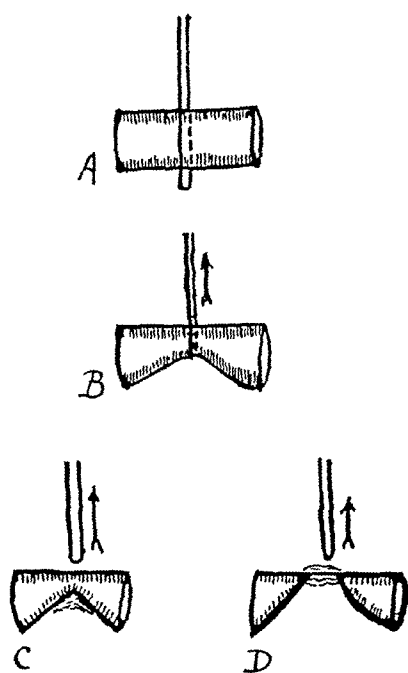


Fig. 1.

Fig. 1.—Schematic representation of ligature transection of portal vein. *A*, Ligature passed about portal vein, not tied. *B*, Compression of vein by tugging upon ligature. Eventually ligature transects portal vein, lumen may persist or rapidly re-form (*C*), or there is cicatricial obliteration of the vessel (*D*)

Fig. 2.—Photograph of occluded portal vein necropsy specimen from Dog 42. *L*, Terminal portion of superior mesenteric vein, *g*, termination of gastrosplenic vein. *S*, Site of transection ligature where portal vein has been divided and is here represented as a solid fibrous cord. *P*, Terminal portion of portal vein, *RP*, right branch, *LP*, left branch



Fig. 2

The high incidence of peritonitis encountered may be ascribed to the contamination of the peritoneal cavity through the sinus persisting for several days by virtue of the ligatures about the portal vein, which ligatures passed backward and forward through the laparotomy wounds as the animals moved about their cages, and also were pulled up and allowed to relax intentionally at intervals in the course of bringing about transections of the portal vein.

TABLE II. OCCLUSIONS OF PORTAL VEIN BY TRANSECTION LIGATURE

DOG	LOOPED LIGATURE ABOUT PORTAL VEIN PULLED OUT OF WOUND; TIME AFTER OPERATION	RESULT
Pap.	Ligature not pulled out	Died 9th day, P.O. of peritonitis; ligature in place, portal vein obliterated by old clot
220	Ligature not pulled out	Died 11th day P.O. of peritonitis; ligature had transected portal vein, portal vein occluded (old)
992	Ligature not pulled out	Died 8th day of peritonitis; portal vein occluded
992 B	Ligature not pulled out	Died 9th day; ligature had partially cut through portal vein, small channel still present
11	10th day	Lived 2 days, died of peritonitis; portal vein transected and occluded
Buz.	11th day	Lived 13 days, died of peritonitis; portal vein transected and occluded
Wag.	5th day	Killed 31 days later; portal vein patent, transverse rugae at site of ligature transection
43	11th day	Killed 42 days later; portal vein occluded, ends separated
42	8th day	Killed 41 days later; portal vein occluded, ends separated
27	10th day	Killed 36 days later; portal vein constricted but not occluded
922	9th day	Killed 10 days later; portal vein occluded, ends separated
952	12th day	Killed 30 days later; portal vein patent with transverse rugae at site of ligature
393	10th day	Killed 27 days later; portal vein obliterated

Four dogs (ligature not pulled out), portal vein occluded in three instances.

Six dogs, portal vein transected, ends of vein separated (complete occlusion) with survival.

Three dogs, portal vein constricted, but patent at site of ligature transection, with survival.



Fig. 3.—Photograph of necropsy of Dog 230, thirteen days after excision of portal vein. Condition prior to necropsy was normal. L, Termination of superior mesenteric vein; S, site of portal vein now completely cicatrized; RP, and LP, right and left branches of portal vein, respectively.

C. After ligature transection of the portal vein, a second laparotomy may be performed for excision of a segment of portal vein (Fig 3). Survival is possible because of the collateral venous anastomoses that developed at the time of gradual portal vein occlusion (or stenosis) by the transection ligature (Table III).

TABLE III. OCCLUSION, THEN EXCISION, OF PORTAL VEIN

DOG	TIME AFTER LIGATURE PULLED OUT RESECTION OF PORTAL VEIN WAS PERFORMED	RESULT
223	3rd day	Lived 3 days; died of general peritonitis
230	14 days	Killed 13 days after constricted portal vein was resected; absence of portal vein confirmed
231	10 days	Living: condition normal 7½ months after operation
395	10 days	Living: condition normal 4 months after operation

The fatality in Dog 223 from general peritonitis was possibly due to the fact that resection of the portal vein was carried out only three days after the looped ligature had been pulled out of the abdomen. In the two animals still surviving there is no evidence of ascites; the subcutaneous veins on the abdominal wall are only slightly dilated, and the animals appear to be in good condition.

SUMMARY

A two-stage procedure is described in dogs for the elective resection of the portal vein. At the first operation a linen ligature is passed about the vein, not tied, and long ends brought out of the laparotomy wound to be tied over the animal's back. During each of the succeeding days the ligature is pulled tightly for several seconds; eventually it is pulled out of the wound intact, indicating that it has transected the vein. The latter is thus completely divided or is stenosed at the transection site. During the period of constriction and transection, a collateral portal circulation develops. At the second laparotomy the stenosed or obliterated segment of portal vein may be excised without untoward effects since the collateral circulation has already developed.

REFERENCES

- Bernard, Claude: *Lessons on Diabetes*, Paris, 1877, J. B. Baillière et fils, p. 316.
 Brunschwig, A.: *Surgical Treatment of Carcinoma of the Body of the Pancreas*, *Ann. Surg.* 120: 406-416, 1944.
 Dragstedt, L. R.: *Gradual Obliteration of the Portal Vein as a Substitute for Eck Fistula*, *Science* 73: 315, 1931.
 Elman, R., and Cole, W. H.: *Hemorrhage and Shock as Causes of Death Following Acute Portal Obstruction*, *Arch. Surg.* 28: 1166-1172, 1934.
 Ito, H., and Omi, K.: *Clinical and Experimental Observations on the Surgical Treatment of Ascites*, *Deutsche Ztschr. f. Chir.* 62: 141-183, 1902.
 Neuhof, H.: *Experimental Ligation of the Portal Vein: Its Application to the Treatment of Suppurative Pylephlebitis*, *Surg., Gynec. & Obst.* 16: 481-488, 1913.
 Oré: *Influence of Obliteration of the Portal Vein on Secretion of Bile and Glycogenic Function of the Liver*, *Compt. rend. Acad. Royal d. sc.* 43: 463-467, 1856.
 Solowieff, A.: *Changes in the Liver as a Result of Complete Ligation of the Portal Vein*, *Virchows Arch.* 62: 195-200, 1875.
 Tilmann, H.: *On the Surgical Treatment of Ascites*, *Deutsche med. Wchnschr.* 18: 284-286, 1899.

BLAST INJURY OF THE LUNG

POSSIBLE EXPLANATION OF MECHANISM IN FATAL CASES —AN EXPERIMENTAL STUDY*

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THE problem of blast injuries, including involvement of the lung, which has been emphasized during the present world-wide conflict, first aroused considerable interest in the medical profession at the beginning of the recent Spanish Civil War. However, the occurrence of lung injuries with an intact thorax was described as early as 1761 by Morgagni.¹ Again during World War I fatal casualties with no evidence of external injury were found on the battlefield. In the few post-mortem examinations that were made on these bodies, interest was centered in the petechial hemorrhages found in the brain and spinal cord. However, in work on rabbits subjected to an explosion, Crile² noted hemorrhages produced bilaterally in the lungs. Mairet and Durante³ also observed pulmonary and nervous tissue lesions produced in dogs. In 1924 Hooker⁴ found, while working on experimental shock produced by TNT and gun blasts, that bruises and occasional rupture of the lungs were the only gross post-mortem lesions found in his animals. Interest thus elapsed until the Spanish Civil War, when blast injuries became common and were the subject of articles by Haldane⁵ and Kretzschmar.⁶ Active investigation of this problem started during the indiscriminate bombing of cities during World War II.

NATURE OF BLAST

The term "blast" may be divided into two components: compression wave and subsequent suction wave which are set up by the detonation of high explosives. At a point in the region of the explosion there occurs first a momentary wave of high pressure (about .006 second for a seventy-pound charge) which is then followed by a negative "suction" wave due to the positive compression wave reducing the density of the air behind it to below normal atmospheric pressure. The suction component is like the pressure component of the blast wave in that it lasts for a fraction of a second. However, it is a far longer period than the compression wave (0.03 second for a seventy-pound charge). The pressure component of the wave is by far the strongest component of the blast. Thus, fifteen feet from a 125 pound charge, the hydrostatic pressure may be approximately 200 pounds per square inch. Whereas the suction component is much weaker, and in no case can it be greater than 125 pounds per square inch, since this corresponds to a complete vacuum (Zuckerman).⁷

THEORIES REGARDING THE EFFECT OF BLAST ON ANIMALS AND HUMAN BEINGS

Zuckerman, working on the effect of blast on animals, reviewed the three following theories used to explain the production of injuries, and rejected the

This paper was to have been presented at the meeting of the Society of University Surgeons, New York, N. Y., Feb. 8, 1945. (Meeting canceled.)

*This work was supported in part by a grant from the Douglas Smith Foundation for Medical Research of The University of Chicago.

first two. First, the lesions are due to the lowering of alveolar pressure by the suction waves, acting through the respiratory passages, with the consequent rupture of alveolar capillaries (suggested by Logan in 1939).⁸ Second, the sudden distention of the lung with air through the trachea causes a rupture of the lung tissue. Third, the injury is caused by a pressure wave on the chest wall. The latter mechanism is advocated by Hooker and Zuckerman. Hooker's view was that it is wholly improbable that lowered pressure could distend the lung sufficiently to cause rupture. The work of Zuckerman and his associates in 1940 to 1942 shows good evidence that the last theory most likely explained the cause of injury to the lungs, this being based on the following:

1. "When animals are exposed sideways and close to a small explosion, the lesions are unilateral, and on the side facing the explosion. When placed farther from the charge the lesions are bilateral. Presumably shielding occurs close to the explosion.

2. "The disposition of lesions in the part of the lung relating to the costo-mediastinal and phrenicocostal sinuses suggests that they are due to external 'blows.'

3. "Lesions occur in abdominal and other organs as well as in the lungs.

4. "Animals exposed to low blast pressures close to a small explosion with their trunks clothed in thick sponge rubber suffer less severely than control animals. Others exposed near the explosion with only one side of the trunk covered in rubber and with the covered side facing the explosion suffer no injury or only very slight injury to the lungs. When exposed with the uncovered side to the explosion they suffer severe damage to the lung of that side, and less severe damage to the lung of the opposite side."

5. Rabbits in both wooden boxes and steel cylinders through which only their heads projected were exposed head-on very close to a big charge. Only those in wooden boxes where the box collapsed showed evidence of pulmonary damage.

PATHOLOGIC FINDINGS

In animals subjected to a depth charge (blast) the most important structural changes were found in the respiratory system. Williams⁹ used a total of twenty-one animals which were subjected to a depth charge (320 pounds of TNT) suspended at forty-eight feet in water to a depth of ninety feet. These animals were distributed from a point directly over the depth charge to as far as 300 yards away. Some animals had the chest protected with rubber, while in others the abdomen was protected. He found that greater hemorrhages occurred in the chest in animals with the chest protected and the abdomen unprotected than was the case when the reverse was true. Eleven of the thirteen animals located within a radius of forty yards of the depth charge were killed immediately. Ten of the eleven had acute interstitial emphysema and three had pneumothorax. All thirteen animals showed pulmonary hemorrhages (five severe, five moderate, three slight). Cameron and his associates¹⁰ thus reported that severe hemorrhages may occur without immediate death, whereas other animals may be killed at once and not show marked pulmonary lesions. The areas most commonly affected by the blast are the anterior borders of the lungs which become pressed between the ribs of the chest wall and the mediastinum, and the inferior borders which become compressed in the costophrenic sinus (Zuckerman). Two other common sites are the costal surfaces and mediastinal areas.

Zuckerman states that the axygos lobe which passes from the root of the right lung across the midline behind the heart is commonly involved. Of Zuckerman's animals which died, none revealed evidence of external injuries. The predominant lesion was bilateral traumatic hemorrhages in both lungs, varying in degree according to the distance of the animal from the explosion.

MICROSCOPICALLY

The lesser degree of damage appeared as small zones in which alveoli and terminal air passages were filled with blood. The walls of the alveoli were often torn and hemorrhages arose from the capillaries of the alveolar walls. In severe damage, larger areas were involved. The cause of death could not be determined from this study.

Hadfield and associates¹¹ stated that microscopic sections made from human autopsies revealed changes similar to those produced by Zuckerman in dogs. These consisted of hemorrhages into alveoli, acute vesicular and interstitial emphysema, and subpleural bullae. One patient had both mediastinal and subcutaneous (neck) emphysema. Two had pericardial emphysema. He stated that of the ten patients considered to have died from blast injury, the pathologic findings were not severe enough to explain the cause of death.

Wilson¹² and others described essentially the same microscopic picture in blast cases as that reported by Hadfield.

In some recent experiments on the production of emphysema by overdistention of the lung with increased intrabronchial pressure it was noted by one of us (R.A.R.) that if the dogs coughed and thus increased the pressure, they suddenly died. At autopsies it was noted that air emboli were present in the coronary vessels. This finding stimulated the following investigation.

EXPERIMENTAL METHODS AND PROCEDURES

Eighteen mongrel dogs were subjected to an increased intrabronchial pressure. The dogs were divided into two groups: The first group of eight dogs was subjected to pressures of from 35 to 50 mm. of mercury for a period of a few seconds to fifteen minutes. The second group of ten animals was subjected to a "blast" varying from 70 to 110 mm. of mercury. Of the group, two animals received a blast of 120 and 240 mm. of mercury, respectively.

Apparatus.—The apparatus used for Group 1 consisted of a modified windshield wiper which was attached to an air jet. The wiper was so built that the length of the inspiratory period, pressure under which the air was delivered, and rate per minute could be easily adjusted (Rasmussen and Adams¹³). A large rubber tube led from the apparatus to the lower trachea. Inside this tube was a smaller rubber tube connecting a mercury manometer with the lower trachea. This double rubber tubing was then passed through a tight-fitting face mask (and an airway) and down the trachea to a point just above the carina. On this mask was an outlet for adjusting intratracheal pressure.

The apparatus used for Group 2 consisted of the same double rubber tubing, airway and face mask, but instead of the wiper apparatus the source of air pressure was connected directly to the large tube. The mercury manometer served also as a check valve for regulating the amount of intratracheal pressure.

The experiment was carried out as follows: A dog was given an injection of 10 c.c. of morphine sulfate (0.15 Gm.) subcutaneously fifteen to thirty minutes before the animal was exposed to the overinflation or "blast." The animal

was then placed in a supine position on the table and a towel was wrapped snugly about its abdomen. Under direct vision the air tube was introduced into the trachea and a face mask was applied. In Group 1 the air was then turned on at a pressure of between 35 to 50 mm. of mercury and delivered at 28 cycles per minute. In Group 2 the dogs were subjected to blasts of air varying from 70 to 110 mm. of mercury (one dog, 120; one dog, 240).



Fig. 1.



Fig. 2.

Fig. 1 (Dog 98)—Photograph of autopsied specimen of dog following three "blasts" of intratracheal air at 80 mm Hg pressure for two to three seconds. The heart and superior mediastinum seen in the center of the picture are almost covered with blebs of air. This animal also had coronary air embolism, intrapulmonary hemorrhage, and pneumothorax.

Fig. 2 (Dog 966)—Photograph of autopsied specimen of dog following a single intratracheal blast of air at 240 mm Hg pressure for two to three seconds. The coronary arteries contain many air bubbles.

RESULTS

In Group 1 the dogs were subjected to overinflation during which coughing occurred and thus raised the intrabronchial pressure. After an episode of coughing the animals died in a few seconds (see Table I). Animals in Group 2 were subjected to blast using apparatus 2. Following the blast these animals died within a few seconds to three minutes (see Table II).

Post-Mortem Observations.—

Group 1, eight dogs—gross findings: All of the eight animals had mediastinal and interstitial emphysema, while four had subcutaneous emphysema and hemorrhages into the lungs. Three of the dogs had developed a pneumothorax and exhibited air in the pulmonary artery, vein, venae cavae, and right auricle. Small bullae were found over the lung in one, and *coronary air embolism* was present in seven, instances.

TABLE I. RESULTS FOLLOWING REPEATED INTRATRACHEAL BLASTS OF AIR OF A KNOWN PRESSURE IN EIGHT DOGS

BLAST					RESULTS					
EXP.	DOG NO.	DURATION (IN MIN.)	RATE (PER MIN.)	PRESSURE (MM. HG)	SUBQ. EMPH.	PNEUMO. THORAX	PUL. HEMORR.	MED. & INT. EMPH.	CORONARY AIR EMBOL.	REMARKS
1	496	15	28	35*	-	+	-	+	-	Dilation of stomach
2	682	1	28	35 to 40*	+	-	+	+	+	Air in pulmonary artery, vein, vena cava
3	683	8	28	35 to 40*	+	-	+	+	+	Air in pulmonary artery, vein, vena cava
4	711	5	28	35*	-	+	+	+	+	Air in pulmonary artery, vein, vena cava
5	67	7	28	30 to 35 C, 100	-	-	-	+	+	
6	68	15	28	35 to 40 C, 50	-	-	-	+	+	Small blebs over lung
7	118	15	28	30 to 35 C, 50	+	+	-	+	+	
8	949	7	28	30 to 50 C, 120	+	-	+	+	+	Air in right auricle and pulmonary vein
Total					4	3	4	8	7	

C, cough
Subq., subcutaneous
Emph., emphysema
Pul., pulmonary
Hemorr., hemorrhage
Med., mediastinal
Int., interstitial
Embol., embolism
*Coughing

TABLE II. RESULTS FOLLOWING SINGLE BLAST OF AIR INTO THE TRACHEA IN TEN DOGS

EXP.	DOG NO.	BLAST			RESULTS					REMARKS
		DURATION OF EACH BLAST (SEC.)	NUMBER	PRESSURE (MM. HG)	SUBQ. EMPH.	PNEUMO. THORAX	PUL. HEMORR.	MED. & INT. EMPH.	CORONARY AIR EMBOL.	
1	3	2 to 3	1	80	-	+	+	+	-	Small blebs over lungs
2	966	2 to 3	1	240	+	+	+	+	+	
3	714	2 to 3	1	80						
		2 to 3	4	85						
		2 to 3	2	90						
		2 to 3	1	95						
		2 to 3	1	100						
4	23	2 to 3	1	110	-	+	+	+	-	Dilation of the stomach
		2 to 3	2	80	+	+	+	+	+	Large blebs over the lung—one large one ruptured
		2 to 3	2	88						
5	50	2 to 3	2	86	-	+	+	+	+	Pneumonectomy previously
6	24	2 to 3	2	80	+	-	-	+	+	
7	97	2 to 3	1	70	+	+	-	+	+	Air in pulmonary vessels, right auricle, vena cava
8	98	2 to 3	3	80	+	+	+	+	+	
9	45	2 to 3	2	80	+	+	+	+	+	
		2 to 3	3	85						
		2 to 3	2	90						
10	993	2 to 3	1	90	+	+	+	+	+	
Total					7	9	8	10	8	

Subq., subcutaneous
Emph., emphysema
Pul., pulmonary
Hemorr., hemorrhage
Med., mediastinal
Int., interstitial
Embol., embolism

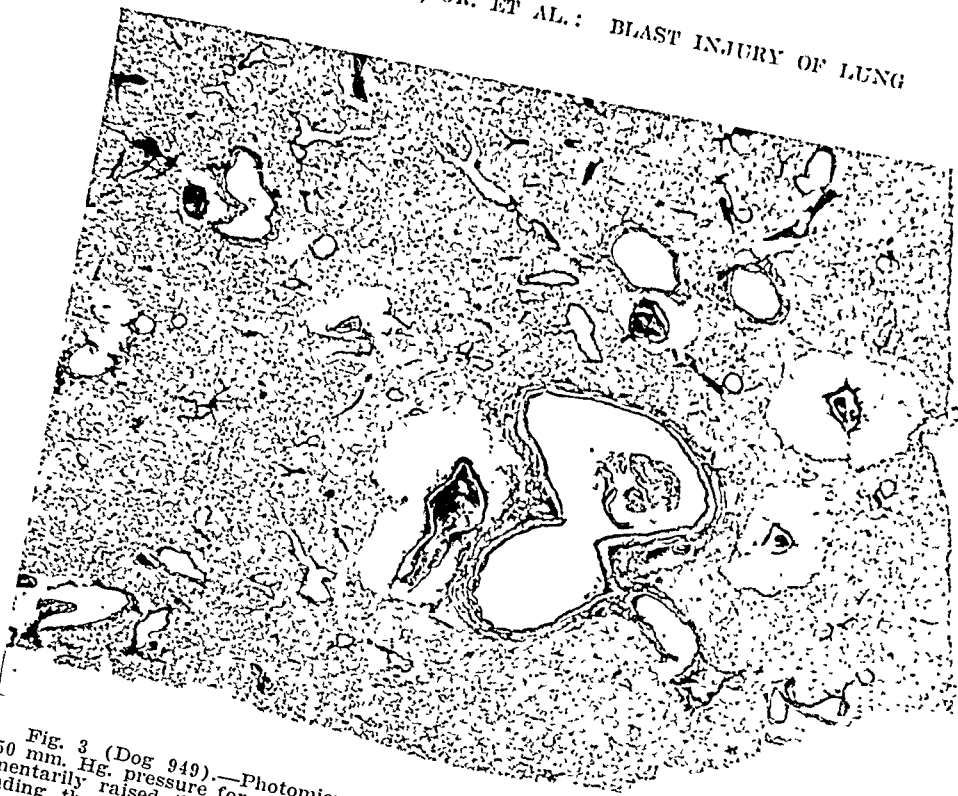


Fig. 3 (Dog 949).—Photomicrograph of lung following overinflation of the lung at 30 to 50 mm. Hg. pressure for seven minutes; at the end of this time the animal coughed, which momentarily raised the pressure to 120 mm. Hg. Note marked interstitial emphysema surrounding the blood vessels especially near the bronchial passages. The animal presented evidence of coronary air embolism as well as air in the right auricle and pulmonary vein.

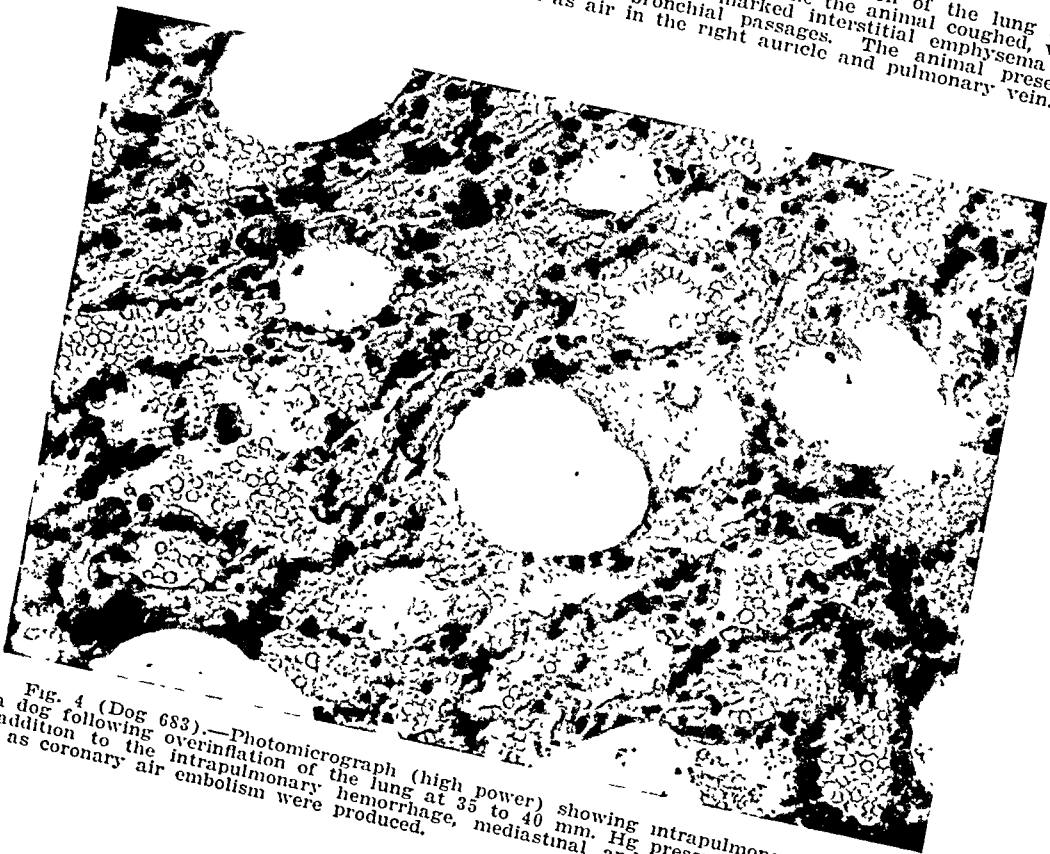


Fig. 4 (Dog 683).—Photomicrograph (high power) showing intrapulmonary hemorrhage in a dog following overinflation of the lung at 35 to 40 mm. Hg. pressure for eight minutes. In addition to the intrapulmonary hemorrhage, mediastinal and interstitial emphysema as well as coronary air embolism were produced.

Group 2, ten dogs—gross findings: All ten animals had developed mediastinal and interstitial emphysema, of which seven had subcutaneous emphysema. Nine had bilateral pneumothorax, while eight showed pulmonary hemorrhages and *coronary air embolism*. One of the dogs developed air in the large vessels (vena cava and right auricle), one had a dilated stomach, and two presented bullae over the lung.

Microscopic sections revealed intrapulmonary hemorrhages and interstitial emphysema, the latter especially marked along the bronchovascular roots.

From these findings the cause of death in all animals was attributed to coronary air embolism and pneumothorax. In Group 1, seven of the dogs had air embolism, whereas three had a pneumothorax. In Group 2, coronary air embolism was present in eight instances and a pneumothorax in nine. The autopsy material presented a picture similar to that reported in patients dying immediately from a blast injury in which the cause of death was unexplained.

DISCUSSION

According to Wilson there have been four main theories advanced for the cause of death due to blast. (1) Death due to pulmonary hemorrhage and interference with the respiratory function. Examinations show that this might be true in some blast cases. The lung injury, however, is usually not sufficient to cause death. (2) Cerebral cause of death. The lesions found in the brain in those patients dying immediately or soon thereafter are very indefinite. (3) Death due to blast may be cardiac in origin. Wilson has stressed the importance of injury to the heart, and that ventricular fibrillation may occur and account for death in some cases. (4) Air embolism may be a possible cause of death.

Zuckerman states that those animals which are immediately killed without sign of external injury probably die of an undefined entity known as "primary shock," resulting from extensive visceral lesions. From reports it is obvious that some patients die of pneumothorax following the blast; however, another group shows very little to account for death. It seems possible to us that death in this latter group might be due to coronary air embolism. In our animal experiments a very careful search was frequently necessary in order to detect air in the coronary vessels. This suggests that the finding could be easily overlooked.

In experimental work, Macklin¹⁴ has demonstrated the course taken by the air and gases in the production of mediastinal emphysema and other complications from overdistention of the lungs by increased intratracheal pressure. He believes, as do others, that air breaks through the terminal alveoli and follows the course of the vessels in the paravascular sheath of the lungs to the mediastinum and thus into the neck and subcutaneous tissue. From these ruptured alveoli it is easy to explain how air can go into the capillaries of the lung, thus forming numerous fistulas. By this means air may pass into the left auricle, ventricle, and the coronary arteries. At times air was also found in the pulmonary artery and right heart. This was probably due to the backing of air into these vessels from the lung. Since the pressure in the pulmonary circulation is only 20 to 40 mm. of mercury, air could easily be forced back through the pulmonary artery.

Upon reviewing the literature a report of experiments by Joannides and Tsoulos was found. The effects of increased intratracheal pressure observed by these authors were similar to those described.

SUMMARY

The cause of death following increased intrabronchial pressure produced by single or multiple blasts of air in eighteen dogs was coronary air embolism in fifteen, with pneumothorax as a contributory factor in eight. Pneumothorax appeared to be the sole cause of death in the remaining three. Other gross findings noted in these animals were similar to those reported in human beings following blast injury. In some patients dying immediately following a blast injury the cause of death has not been adequately explained. Coronary air embolism may be very easily overlooked and might well be the cause of death in some cases of blast injuries.

REFERENCES

1. Morgagni, J. B.: *De Sedibus et Causis Morborum per anatomen Indagatis Venetiis*, 1761; Quoted by King, J. D., and Curtis, G. M.: *Surg., Gynec. & Obst.* 74: 53, 1942.
2. Crile, George: *Official History of the War Medical Services, Surgery of the War* 1: 47, 1922.
3. Mairet, A., and Durante, G.: *Etude experimental du syndrome commotionnelle*, *Presse méd.* 25: 478, 1917.
4. Hooker, D. R.: *Physiological Effects of Air Concussion*, *Am. J. Physiol.* 67: 219, 1923-24.
5. Haldane, J. B. S.: *Air Raid Precautions*, London, 1938, V. Gollancz Ltd.
6. Kretschmer, C. H.: *Wounds of the Chest Treated by Artificial Pneumothorax*, *Lancet* 1: 832, 1940.
7. Zuckerman, S.: *Experimental Study of Blast Injuries to the Lungs*, *Lancet* 2: 219, 1940. *Ibid*: *Discussion on the Problem of Blast Injuries*, *Proc. Roy. Soc. Med.* 34: 171, 1941. Zuckerman, S., Krohn, P. L., and Whitteridge, D.: *Physiological Effects of Blast*, *Lancet* 1: 252, 1942.
8. Logan, D. D.: *Detonation of High Explosive in Shell and Bomb and Its Effects*, *Brit. M. J.* 2: 864, 1939.
9. Williams, E. R. P. (Surgeon Commander): *Blast Effects in Warfare*, *Brit. J. Surg.* 30: 38, 1942-43.
10. Cameron, G. R. (Major) Short, R. H. D., and Wakeley, C. P. G. (Surgeon Rear Admiral): *Pathological Changes Produced in Animals by Depth Charge*, *Brit. J. Surg.* 30: 49, 1942-43.
11. Hadfield, G., Ross, J. M., Swain, R. H. A., and Drury-White, J. M.: *Blasts From High Explosives*, *Lancet* 2: 478, 1940. Hadfield, G.: *Discussion of Problem of Blast Injury*, *Proc. Roy. Soc. Med.* 34: 189, 1941.
12. Wilson, J. V.: *The Pathology of Closed Injuries of the Chest*, *Brit. M. J.* 1: 470, 1943.
13. Rasmussen, R. A., and Adams, W. E.: *Experimental Production of Emphysema*, *Arch. Int. Med.* 70: 379, 1942.
14. Macklin, C. C.: *Pneumothorax With Massive Collapse From Experimental Local Over-Inflation of Lung Substance*, *Canad. M. A. J.* 36: 414, 1937.
15. Joannides, M., and Tsoulos, G. D.: *The Etiology of Interstitial and Mediastinal Emphysema*, *Arch. Surg.* 21: 33, 1930.

METABOLIC ALTERATIONS FOLLOWING THERMAL BURNS

IV. THE EFFECT OF TREATMENT WITH WHOLE BLOOD AND AN ELECTROLYTE SOLUTION OR WITH PLASMA FOLLOWING AN EXPERIMENTAL BURN²

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APPROXIMATELY eight years ago plasma was first employed to combat shock resulting from a burn. Since that time it has been widely employed but only recently has its value been questioned. Rosenthal¹ demonstrated a better survival rate in burned mice which received a physiologic solution of sodium chloride by mouth than in mice with a similar burn given serum intravenously. Fox² advocated the use of a sodium lactate solution orally, and discussed some of the inadequacies of plasma. More recently Moyer, Collier, Job, Vaughan, and Marty³ have felt that defibrinated whole blood and a sodium chloride-bicarbonate solution by mouth proved more effective than plasma, or serum, in treating severely burned dogs. The opposite view is held by Wolf and Levinson,⁴ who have stated "in cases of shock with definite hemoconcentration (trauma with minimal hemorrhage, burns), serum or plasma is superior to whole blood transfusions. In hypoproteinemia serum or plasma is ideal." However, we have noted that in many instances hemoconcentration occurs in burned patients who were treated with large and adequate amounts of plasma. It is true that the blood might have become more concentrated if plasma had not been given; however, hemoconcentration in the burned patients treated with whole blood and oral salt solution simultaneously has not been more severe than in those who were treated with plasma, unless the salt solution was temporarily withheld or was not absorbed. It has also been frequently observed that the plasma protein concentration decreases† in severe cases in spite of the administration of plasma in amounts which (by any of the commonly employed methods of governing this type of therapy) have been considered adequate.

In a previous publication⁵ the alterations in the plasma volume, hematocrit, total circulating plasma protein, and albumin during the convalescent phase in burned animals were presented. Following the completion of this work it seemed desirable to determine the effect of treatment with plasma or with whole blood and a salt solution orally on these aforementioned blood studies (plasma volume, hematocrit, red blood cell mass, total circulating plasma protein, and albumin). The studies were undertaken in the hope of further clarifying the metabolism of salt and water in burned animals and to determine whether or not the anemia which occurs during the convalescent phase could be prevented.

METHODS

Normal healthy male dogs who had been given a vermifuge were placed on a previously described diet⁶ for at least one week prior to the control studies

This paper was to have been presented at the meeting of the Society of University Surgeons, New York, N. Y., Feb. 8, 1945. (Meeting canceled.)

²The work described in this paper was done, in part, under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Wayne University. It was supported in part by grants from the Theodore A. McGraw Fund for Surgical Research and from Frederick Stearns and Company.

†Unpublished data.

and burning. During the control and postburn period the intake of food and liquid was measured and the daily output of urine was recorded. The method of producing a relatively standardized burn involving 20 per cent of the body has been previously described.⁵ This method was again employed but in order to determine the effect of a more severe burn, several dogs were studied who received deep third degree burns involving approximately 40 per cent of their body surface area. The animals were given sodium pentobarbital intravenously (0.064 Gm. per five pounds of body weight) and then were burned by placing them on their side for thirty seconds in a large pan containing water which had been heated to 85° C. No further anesthesia or sedatives were employed. The temperature of the water fell 2 to 3 degrees during the period of immersion. The method of determining the plasma and "available (thiocyanate) fluid" volume,⁶ hematocrit, plasma protein, and albumin concentrations and for calculating the blood volume and total circulating plasma protein and albumin have been previously described.⁵ We are aware of the fact that several investigators^{7, 8} have shown that the true blood volume and hence the red cell mass may not be calculated from the plasma volume and the hematocrit, but the relationship of the cells to plasma should be fairly constant in these experiments and it was felt that because of this the per cent change of the red blood cell mass would be of some significance. The electrolyte solution† which was given orally contained the following constituents per liter of distilled water: 6.10 Gm. sodium chloride, 0.20 Gm. calcium chloride, 0.20 Gm. potassium chloride, 0.07 Gm. sodium phosphate (monobasic), 0.05 Gm. magnesium chloride, 2.38 Gm. sodium bicarbonate, and 2.0 Gm. dextrose. Since it has been advocated³ that an amount of sodium chloride-bicarbonate solution equal to 10 per cent of the body weight be given during the first twenty-four hours and a quantity equal to 5 per cent of the body weight during the second twenty-four hours after burning, this solution was employed in a like manner. The animals were transfused with either citrated plasma given slowly and in divided doses so no reactions would be encountered, or with defibrinated whole blood. When plasma was given it was decided to employ an amount similar to that advocated by the National Research Council, that is, 50 to 100 c.c. of plasma for every per cent of the body surface area burned, after adjusting it for the difference in weight between man and animal. The following formula was employed to calculate the total amount of plasma to be administered:

$$\frac{\text{Weight of animal}}{\text{Weight of adult male (150 lb.)}} \times \text{per cent of body burned} \times 75 \text{ c.c.} = \text{c.c. of plasma to be given.}$$

When defibrinated whole blood was used, the animal was given an amount equal to about 3 per cent of the body weight within two to four hours after burning and an amount equal to 2 per cent of the body weight sixteen to twenty hours after burning. No therapy, either oral or intravenous, was given until one and one-half hours after the burn. The animals, which were still anesthetized, were then given one-fourth to one-third of their daily fluid intake by stomach tube and shortly thereafter received the initial plasma or defibrinated whole

*The dye, T-1824, and the 5 per cent sodium thiocyanate solutions employed were kindly prepared in ampules furnished by the Kimble Glass Company, by members of the College of Pharmacy of Wayne University.

†It was thought advisable to employ a salt solution which had an electrolyte concentration somewhat similar to that of plasma with the exception that the amount of potassium chloride was decreased since the plasma potassium concentration is known to increase following a burn. This solution was kindly prepared for us in sterile ampules by Sharp & Dohme Inc.

TABLE I. RESULTS ON ANIMALS TREATED WITH PLASMA INTRAVENOUSLY

DOG NO. AND PER CENT OF BODY BURNED	DAYS POST- BURN	PER CENT CHANGE IN WEIGHT	PLASMA VOLUME		PER CENT CHANGE IN TOTAL CIRCULATING PLASMA PROTEINS		HEMATO- CRIT	PER CENT CHANGE IN RED CELL MASS	“AVAILABLE (THIOCYANATE) FLUID,” VOLUME	
			PER CENT CHANGE	PER CENT CHANGE PER KILOGRAM	PLASMA PROTEIN	PLASMA ALBUMIN			PER CENT CHANGE	PER CENT PER KILOGRAM
No. 57 20%	0	(11.3 kg.)	(691 c.c.)	(61 c.c.)	(40.0 Gm.)	(21.1 Gm.)	43.1	(530 c.c.)	(4,223 c.c.)	(373 c.c.)
	4	- 3	+20	+23	+19	- 2	37.8	- 5	+ 9	+12
	9	-20	+ 1	+26	+ 8	-15	39.7	-13	-11	+12
No. 122 20%	0	(14.6 kg.)	(716 c.c.)	(49.2 c.c.)	(40.7 Gm.)	(21.9 Gm.)	56.1	(926 c.c.)	(4,718 c.c.)	(326 c.c.)
	4	- 1	+34	+33	+36	+ 9	46.1	-13	+13	+11
	9	- 9	+34	+13	+26	-25	40.3	-32	-11	+25
No. 61 40%	19	-17	+18	+43	+43	- 9	45.2	-25	+ 5	+26
	0	(19.1 kg.)	(946 c.c.)	(49.8 c.c.)	(56.5 Gm.)	(31.9 Gm.)	17.1	(812 c.c.)	(6,679 c.c.)	(351 c.c.)
	4	+ 7	+34	+24	+36	+28	39.0	- 4	+22	+13

TABLE II. RESULTS ON ANIMALS TREATED WITH BLOOD INTRAVENOUSLY AND AN ELECTROLYTE SOLUTION ORALLY

DOG NO. AND PER CENT OF BODY BURNED	DAYS POST- BURN	PER CENT CHANGE IN WEIGHT	PLASMA VOLUME		PER CENT CHANGE IN TOTAL CIRCULATING PLASMA PROTEINS		HEMATO- CRIT	PER CENT CHANGE IN RED CELL MASS	“AVAILABLE (THIOCYANATE) FLUID,” VOLUME	
			PER CENT CHANGE	PER CENT CHANGE PER KILOGRAM	PLASMA PROTEIN	PLASMA ALBUMIN			PER CENT CHANGE	PER CENT CHANGE PER KILOGRAM
No. 52 20%	0	(12.1 kg.)	(602 c.c.)	(49.9 c.c.)	(42.9 Gm.)	(21.6 Gm.)	58.1	(835 c.c.)	(3,615 c.c.)	(300 c.c.)
	4	- 2	+22	+25	+14	+ 8	56.7	+15	+15	+18
	9	- 9	+15	+26	+ 1	-30	51.8	0	+17	+28
No. 111 20%	21	-20	0	+25	- 4	-31	56.1	- 8	- 1	+23
	0	(14.2 kg.)	(743 c.c.)	(52.5 c.c.)	(47.1 Gm.)	(29.7 Gm.)	58.0	(1,026 c.c.)	(4,580 c.c.)	(324 c.c.)
	4	0	- 3	- 4	+ 5	- 9	62.6	+17	+ 6	+ 6
No. 59 40%	9	- 9	- 4	+ 6	- 5	-31	59.9	+ 4	0	+10
	21	-15	- 8	+ 8	- 4	-29	58.8	- 5	+ 1	+15
	0	(12.8 kg.)	(547 c.c.)	(43.0 c.c.)	(32.7 Gm.)	(20.4 Gm.)	53.0	(618 c.c.)	(3,838 c.c.)	(301 c.c.)
No. 60 40%	4	+ 5	+24	+19	+17	-23	57.5	+49	+28	+22
	0	(15.0 kg.)	(780 c.c.)	(52.0 c.c.)	(45.9 Gm.)	(27.2 Gm.)	50.8	(805 c.c.)	(4,886 c.c.)	(325 c.c.)
	4	+21	- 2	-19	-18	-29	56.6	+24	+60	+33

blood transfusion. Two animals were transfused with red cells obtained from fresh blood drawn from suitable donor dogs. After the blood was centrifuged and the plasma removed, the red cells were given immediately without the addition of any diluent.

RESULTS

The food intake of the control animals and of those which received specific shock therapy remained constant both before and after burning in almost every instance. However, soon after burning, all of the animals spontaneously doubled or tripled their fluid intake. The urine output was often reduced or normal on the first day but subsequently rose to two or three times the amount excreted during the control period and, like the fluid intake, approached normal in about fifteen days. The type of therapy employed did not seem to alter the food and fluid intake or the urine excretion in the different groups studied.

The alterations in the previously presented series⁵ showed that nontreated burned animals during the postshock phase had a fairly marked and persistent elevation in their plasma volumes, increases in the total circulating plasma proteins, and a moderate anemia. These changes persisted for at least one month.

It was also observed that, after an initial rise, the total circulating plasma albumin decreased and that the magnitude of the plasma volume was not dependent on the plasma protein or albumin concentration.

In the control animals, four days after burning, the average weight loss was 4 per cent below the control level, at nine days it was 10 per cent, at thirteen days, 12.5 per cent, and at twenty days, 15 per cent below the control figure.

The results in the animals treated during the shock phase with plasma are presented in Table I. The alterations noted in these dogs were not unlike those seen in the control animals with the possible exception that the plasma volume was slightly higher. Dog 57 first refused food and water on the fifth day, lost weight rapidly, and on the ninth day appeared to have distemper. Since other animals had been studied which refused food and water, vomited, or had diarrhea, it was felt that the response of this dog, while not typical of burns alone, was of interest. As in one of the control animals with diarrhea, this dog showed a rapid diminution in the body weight and plasma volume. By the ninth day, the animal's condition was so serious that it was sacrificed. Dog 61 showed a marked increase in body weight on the fourth day, which was due to retention of water. The increase in body weight was almost equivalent to the increase in the "available (thiocyanate) fluid" volume.

The results of treatment with whole blood intravenously and with salt solution by mouth are presented in Table II. In these animals the hematocrit remained at normal levels throughout and the marked decrease in the red blood cell mass seen in the control and plasma treated dogs did not occur. The per cent change in the red cell mass showed an increase above the control value followed by a gradual fall to near normal by the twentieth day. No constant findings were noted in the plasma volume determinations in these animals and the changes which occurred in the total circulating plasma protein and albumin were not unlike the findings encountered in the control animals. Dog 60 and, to a lesser degree, Dog 59 showed a marked increase in weight, which was due to the accumulation of large amounts of fluid in the burned areas and to a

TABLE III. RESULTS ON ANIMALS WHO AFTER EXHIBITING THE USUAL CHANGES WERE TRANSFUSED WITH RED BLOOD CELLS

DOG NO. AND PER CENT OF BODY BURNED	DAYS POST- BURN	PER CENT CHANGE IN WEIGHT	PLASMA VOLUME		PER CENT CHANGE IN TOTAL CIRCULATING PLASMA PROTEINS			HEMATO- CRIT	PER CENT CHANGE IN RED CELL MASS	"AVAILABLE (THIOCYANATE) FLUID," VOLUME	
			PER CENT CHANGE KILOGRAM	PER CENT CHANGE KILOGRAM	PLASMA PROTEIN	PLASMA ALBUMIN	PLASMA GLOBULIN			PER CENT CHANGE	PER CENT CHANGE PTR KILOGRAM
No. 16 17%	0	(12.5 kg.)	(69.1 c.c.)	(55.7 c.c.)	(40.7 Gm.)	(24.8 Gm.)		52.6	(770 c.c.)	(4,580 c.c.)	(367 c.c.)
	5	- 2	+ 9	+11	+ 1	0		44.8	-20	+11	+13
	8	- 4	+12	+19	- 2	+ 5		39.5	-34	+ 1	+ 6
Transfusions											
No. 17 17%	14	- 9	+11	+21	+10	+ 6		53.5	+15	+ 6	+16
	19							44.1			
	22	-11	+ 1	+17	- 2	-23		42.3	-33		
	33	-15	0	+17	- 7	-15		44.4	-28	- 1	+13
	0	(14.2 kg.)	(652 c.c.)	(46.0 c.c.)	(36.8 Gm.)	(20.5 Gm.)		50.0	(652 c.c.)	(3,735 c.c.)	(261 c.c.)
	5	- 6	+ 6	+13	+12	+30		42.2	-22	+18	+26
	8	-10	+17	+20	+15	+42		37.0	-31	+11	+22
Transfusions											
	14	-15	+ 9	+28	+12	+19		47.1	- 3	+ 1	+22
	19							40.8			
	22	-20	+ 9	+32	+ 8	- 7		35.0	-11	+13	+41
	33	-26	+ 5	+38	+27	- 5		35.9	-11	+ 8	+45

lesser extent in the nonburned areas. These two animals were apparently given too much salt solution. They received amounts equaling about 2½ per cent of their body weight on the third and fourth days besides the initial two days of therapy. This increase in weight again can, in a large part, be accounted for by the increase in the extracellular fluid compartment, as shown roughly by the thiocyanate determination. In Dog 60, treatment was started in the usual fashion about one and one-half hours after burning; he received a whole blood transfusion (490 c.c.) and a relatively small amount of the electrolyte solution by stomach tube. No further therapy was given nor water permitted until twenty hours after the burn. The hematocrit at this time had risen from a control value of 53 to 73 and the animal had obviously had insufficient amounts

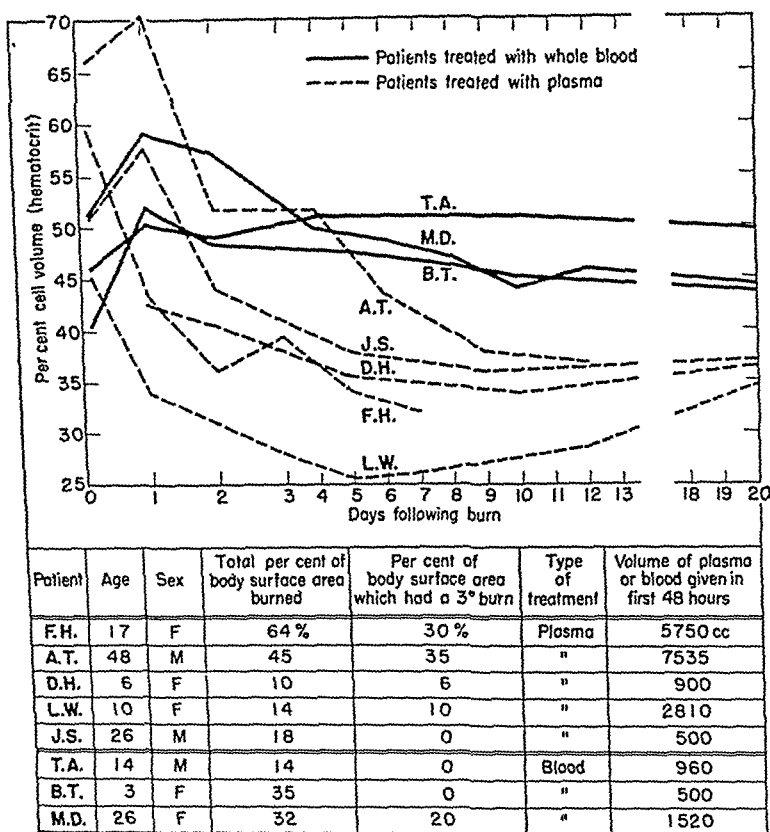


Fig. 1.—Response of the hematocrit in burned patients treated with whole blood or plasma.

of the salt solution. When he was permitted to drink this solution, even though more whole blood (330 c.c.) was then administered, the hematocrit soon fell to the control level.

In Table III the results are presented on two animals which after burning showed the usual increase in the plasma volume and fall in the hematocrit and in the red cell mass. Following the studies on the eighth day, each animal was given a fresh red cell transfusion every other day for three times, making a total of 285 c.c. of red cells, which was more than adequate to correct their deficit. The plasma was purposely omitted because of an already existing increase in plasma volume. Approximately sixteen hours after the last transfusion was completed, the plasma volumes showed a very slight decrease from the previous level and there was marked increase in the red cell mass. Subsequent studies showed that the anemia recurred quite rapidly and by twenty-

two days was as severe as that exhibited by the nontreated control animals in twenty days. When the anemia was recurring, the plasma volume continued to decrease toward the normal value.

Since the healing of the wounds in the various groups was not significantly altered from the control series and since the number of animals studied was small, it was not possible to say that any one form of therapy was preferable in regard to healing.

The hematocrit alterations that occurred in eight human beings over a period of twenty days following their burns are presented in Fig. 1 (chart and table). The extent of the burn and the type and amount of therapy are described. It should be noted that the patients who received plasma showed a greater decrease in the hematocrit than the patients who received whole blood and a salt solution orally. Patients F. H. and A. T. died on the eighth and thirteenth day, respectively, following their burns. The plasma protein concentration in the cases presented decreased to a greater or lesser extent, and there was no evidence to show that the administration of plasma aided in maintaining a normal protein or albumin concentration. The hematocrit in patient M. D. decreased after twenty-five days. At this time she had a fairly large area of third degree burn which was still not healed. Because she had rheumatic heart disease and had been decompensated several times, she was given only 1,500 c.c. of blood (an amount equal to 3 per cent of her body weight).

DISCUSSION

The most striking difference in the late effect of the two types of therapy pertains to the hematocrit and the circulating red cell mass. Both the untreated control animals and those which received plasma exhibited a marked decrease in the circulating red cells which varied from minus 12 to minus 27 per cent in the control animals and from minus 13 to minus 32 per cent in the plasma-treated group on the ninth day after burning. This fall did not occur in the animals which received whole blood transfusions.

The cause of the anemia seen during the convalescence from burns is not entirely understood, but it does seem apparent that numerous factors play a part. Hemolysis of red cells often occurs at the time of the burn due to the intense heat and may be evident when a sample of blood is drawn several hours later. Subsequently, the slight rise in the icterus index and the presence of increased amounts of blood pigments in the urine verify the previous destruction of red blood cells. Ham⁹ has shown that the congestion of both the larger and smaller blood vessels, together with the small hemorrhages that are commonly observed, account for the loss of whole blood from the active circulation. The present studies show that the increase in the plasma volume causes a dilution in the red cells. (Calculations reveal that the hematocrit would read from 1 to 8 points higher if the plasma volume had remained at the control value.) Harkins¹⁰ has suggested that the anemia may be due to one or more of the following factors: "(a) Reabsorption of fluid, (b) primary destruction and increased fragility, (c) continued destruction of red blood cells and slowing of their formation due to sepsis, bleeding from granulating surfaces and malnutrition." Regardless of the cause, it appears at present that whole blood transfusions given during the first twenty-four hours to burned patients and animals afford the most satisfactory means of preventing the anemia. It is important that the transfusion of whole blood be given at this

time, for if the anemia is permitted to occur, subsequent transfusions are relatively less effective. (This has been noted in patients, and seems evident from the results on Dogs 15 and 16.)

Since it has been stated¹¹ that in the presence of some types of anemia there is a rise in the plasma volume, it was felt possible that the increase observed might be an attempt by the body to compensate for the diminished red cell mass. Because there was not a dramatic change noted in the plasma volume when the red blood cell mass was increased by transfusing red blood cells, and since the plasma volume continued to fall when the anemia recurred, the afore-mentioned theory does not seem to explain the plasma volume alterations which were found in these experiments.

While the animals treated with plasma exhibited a slightly larger increase in their plasma volumes than did the control animals, the number studied was not sufficient to prove this point. Since the magnitude of the plasma volume is not dependent solely on the amount of protein present, but rather, as has been previously stated,⁵ on numerous other factors, we feel that the various changes encountered are not dependent alone upon the type of therapy employed but upon the following factors: (1) The extent and depth of the burn, (2) the time of instituting therapy, (3) the size of the treated subject, and the extent and consistency of the therapy, (4) the individual function of the cardiovascular system and kidneys, and (5) the time of obtaining studies after the injury.

It is also of interest that in some of the animals which were treated with plasma during the shock phase, the decrease in the total circulating albumin was as great or greater than in the control group. Thus, the giving of plasma did not apparently sustain a normal amount of circulating albumin.

Further studies (chloride, CO₂, sodium, and in some cases tissue analysis) were done on some of these animals and on others not included in this paper. These analyses are not complete and will be reported later, but from the information obtained thus far an attempt will be made to clarify the alterations in the water and salt metabolism that are noted in the burned patient.

Selye¹² has stated that during the postshock or "countershock" phase following a burn (or after other injuries where the "alarm reaction" occurs) there is a retention of water and salts due to an increased activity of the adrenal gland. From unpublished data we have noted an elevation in the cortin output in the urine of burned patients, and in severely burned patients and animals a retention of water and salts has been observed.^{13, 14} It is also evident from our work that the convalescent period of burned animals and patients resembles in many respects the course followed by normal animals treated with desoxycorticosterone acetate by Loeb¹⁵ (large water intake, with an increased urine volume but with water retention).

Lyons, Jacobson, and Avery¹⁶ have recently pointed out that the administration of various sodium salts for two days to normal subjects will cause an increase in the plasma volume. In their experiments the plasma protein concentration fell only slightly and, although such was not reported, an increase in the amount of the total circulating plasma protein occurred. Thus, from our work⁵ and that of others,^{17, 18} it is apparent that a normal or fairly well-nourished individual who has an increase in the amount of water and salts in the extracellular fluid compartments will mobilize plasma protein and maintain a relatively normal protein concentration, thereby showing a marked increase in the total circulating plasma protein. Thus, in some post-

operative cases, and in burned patients, the low protein concentration encountered may occur not because of a decreased amount of circulating plasma protein but because of an insufficient amount of available plasma protein (depleted protein reserves) or an excessive retention of water. (The increase in plasma water is greater than the increase in the total circulating plasma protein with a resulting dilution and fall in the plasma protein concentration. If a good diuresis occurs many of the patients studied have shown a definite and fairly rapid rise in their plasma protein concentration.)

Peters and Van Slyke¹¹ have held the same view and state that the protein concentration may be affected either by changing the total amount of circulating protein in the body or by changing the plasma volume so that the proteins are diluted or concentrated.

It has been suggested¹⁸ that sodium chloride should be administered to the burned patient during the convalescent phase, especially if the plasma electrolyte levels show a decrease below the normal concentration. If excessive amounts of salts are lost from the wound, or are lost due to vomiting or diarrhea, such therapy would be indicated, but if the patient is given plasma, whole blood, or an oral salt solution in adequate amounts during the first several days and does not have large losses, he should have a sufficient amount of the necessary electrolytes to more than replace these deficits.

In many burned patients during the convalescent phase the fall in the blood electrolyte concentration (chloride and sodium) is again due to a greater retention of water than of salts. Many of the animals studied have shown an increase in their extracellular fluid volumes and a low plasma chloride concentration. Such levels may not be corrected by the administration of an isotonic or hypotonic salt solution, but rather they would return to normal if the excess water was removed. (This might be accomplished by withholding water temporarily and administering a hypertonic salt solution or by giving a concentrated plasma or albumin solution. The use of suitable diuretics may also be of value.)

The low plasma chloride concentrations encountered in intestinal obstruction¹⁹ and other similar disorders are, of course, due to an actual decrease in extracellular salts; on the other hand, the low levels encountered in burns and in many patients with malnutrition edema are usually due to a greater retention of water than salts. The patient in the first type of case, when given a physiologic solution of sodium chloride, would show a fairly rapid return to the normal plasma concentrations of chloride and sodium, while the latter group of patients would show an increase in the extracellular fluid volume, but very little alteration in their blood concentrations. We do not wish to leave the impression that salt deficiencies may not occasionally occur in such patients during the convalescent phase, but rather to emphasize the fact that a low plasma sodium or chloride concentration can be encountered when the body has excessive amounts of these elements and that therapy should not be guided solely by such values.

It has been pointed out²⁰⁻²² that when low concentrations of sodium are encountered in the extracellular fluid there is an intracellular shift of water with resulting cellular edema. It has also been shown^{3, 23} that when excessive amounts of water are given to even mildly burned animals a marked fall in the plasma chloride concentration occurs, and water intoxication and death may result. Since the symptoms of water intoxication (rising temperature and pulse, mental confusion, coma, etc.) as described by Trusler, Egbert, and Williams²³

are fairly frequently encountered in fatally burned patients, it seems as though a state of overhydration should be guarded against during the postshock period.

In Dog 60 and in one patient treated with whole blood and the salt solution by mouth, the hematocrits rose to 73 and 76, respectively; however, in both instances there was an inadequate amount of salt solution given initially. The clinical course in the afore-mentioned animal and patient in whom treatment was unavoidably delayed was significant. The animal showed the most profound edema of any one studied, before being sacrificed, and the patient who had a very extensive third degree burn succumbed after seven days.

Green and Bergeron²⁴ have felt that in tourniquet shock some toxic substance apparently accumulates which ultimately causes death. Because of the local loss of fluid into the traumatized area and hence a reduction in the blood volume, he believes that the kidneys are unable to eliminate this substance. In his cross-transfusion experiments, when a normal blood volume and urine excretion were maintained in the control animal, no ill effects were noted in the control group, but in similar control animals when the ureters were ligated, death of the control animal occurred quite promptly. This would appear to indicate that the fluid lost and the presence of a toxic substance were of great importance. If such is the case in burned patients, it would seem that an early restoration of the blood volume and urine flow were of the utmost importance. Since an adequate blood volume and urine flow can be obtained*² by employing adequate amounts of a suitable electrolyte solution, and since the plasma protein and albumin concentrations are often not maintained by plasma transfusions except possibly during the period of shock, it seems that such a salt solution may prove to be of even greater value than plasma in the treatment of burned patients.

In other forms of experimental shock,^{25, 26} salt solutions in large amounts have proved to be of value. It also has been noted that the plasma protein concentration falls during this form of therapy but apparently this fall did not impair the chance of survival. The use of concentrated albumin during the convalescent period when the total circulating albumin is low and the body water is increased may prove desirable.

Since whole blood in adequate amounts seems to prevent the anemia which is usually encountered from occurring it would seem wise to administer it in conjunction with the electrolyte solution, in preference to plasma. In second degree burns, where the loss of red cells is not great, smaller quantities of whole blood should be adequate, and in patients with a large third degree burn subsequent small transfusion may be indicated.

CONCLUSIONS

1. By giving whole blood intravenously (amounts equaling up to 5 per cent of the body weight) during the shock phase, the anemia that is encountered during the convalescent period of burned animals or patients has been ameliorated or prevented.
2. When a salt solution is given by mouth with whole blood intravenously during the shock phase following a burn, undue hemoconcentration is not encountered and recovery is satisfactory.
3. Inasmuch as burned animals and patients usually show a marked retention of water during the postshock period, the fall in the plasma protein,

*Unpublished data.

chloride, and sodium concentrations often does not indicate a deficiency of these elements but rather a dilution of them. The decrease noted in the plasma albumin concentration is due not only to dilution but also to an actual decrease as shown by the fall in the total circulating plasma albumin.

The authors wish to express their gratitude for the helpful assistance of William Sugiyama, L. H. Stout, Jr., N. O. Kaplan, Jean Eberly, Mary Allison, Richard Iwata, and Catherine McKay who helped make this work possible.

REFERENCES

1. Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock; III. Effects of Systemic Therapy on Early Mortality. *Pub. Health Rep.* 58: 513-522, 1943.
2. Fox, C. L., Jr.: Oral Sodium Lactate in the Treatment of Burn Shock, *J. A. M. A.* 124: 207-212, 1944.
3. Moyer, C. A., Collier, F. A., Job, V., Vaughan, H. H., and Marty, D.: A Study of the Interrelationship of Salt Solutions, Serum and Desfibrinated Blood in the Treatment of Severely Scalded, Anesthetized Dogs, *Ann. Surg.* 120: 367-376, 1944.
4. Wolf, A. M., and Levinson, S. O.: Human Serum and Plasma: Their Application in Medicine, *M. Clin. North America* 27: 157-188, 1943.
5. Abbott, W. E., Hirshfeld, J. W., and Meyer, F. L.: Metabolic Alterations Following Thermal Burns; II. Changes in the Plasma Volume and Plasma Protein in the Convalescent Phase, *Surg., Gynec. & Obst.* (In press.)
6. Meyer, F. L., Joseph, S., Hirshfeld, J. W., and Abbott, W. E.: Metabolic Alterations Following Thermal Burns; I. Nitrogen Balance in Experimental Burns, *J. Clin. Investigation*. (In Press.)
7. Stead, E. A. Jr., and Ebert, R. V.: Relationship of the Plasma Volume and the Cell Plasma Ratio to the Total Red Cell Volume, *Am. J. Physiol.* 132: 411-417, 1941.
8. Hahn, P. F., Ross, J. F., Bale, W. F., Balfour, W. M., and Whipple, G. H.: Red Cell and Plasma Volumes (Circulating and Total) as Determined by Radio Iron and by Dye, *J. Exper. Med.* 75: 221-232, 1942.
9. Ham, A. W.: Histopathology of Burns, *Ann Surg.* 120: 689-697, 1944.
10. Harkins, H. N.: Recent Research in the Pathology of Burns, *Arch. Path.* 38: 147-154, 1944.
11. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. I, Interpretations, Baltimore, 1931, The Williams & Wilkins Company.
12. Selye, H.: The Alarm Reaction, *Cyclopedia of Medicine*, Vol. 15, Surgery and Specialties, Philadelphia, 1940, F. A. Davis Company, pp. 15-38.
13. Davidson, E. C.: Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy, *Arch. Surg.* 13: 262-277, 1926.
14. McIver, M. A.: Study in Extensive Cutaneous Burns, *Ann. Surg.* 97: 670-682, 1933.
15. Loeb, R. F.: The Adrenal Cortex and Electrolyte Behavior, *The Harvey Lectures*, 37: 100-128, 1941-42.
16. Lyons, R. H., Jacobson, S. D., and Avery, N. L.: Increases in the Plasma Volume Following the Administration of Sodium Salts, *Am. J. M. Sc.* 208: 148-154, 1944.
17. Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure. An Interpretation of the Mechanisms Producing the Edema, Increased Plasma Volume and Elevated Venous Pressure in Certain Patients With Prolonged Congestive Failure, *Arch. Int. Med.* 73: 138-147, 1944.
18. Ficarra, B. J., and Naclerio, E. A.: The Physiochemical Disturbances in a Severe Burn, *SURGERY* 16: 529-541, 1944.
19. Abbott, W. E., Mellors, R. C., and Muntwyler, E.: Fluid, Protein and Electrolyte Alterations in Experimental Intestinal Obstruction, *Ann. Surg.* 117: 39-51, 1943.
20. Eichelberger, L., and Hastings, A. B.: The Exchange of Salt and Water Between Muscle and Blood; III. The Effect of Dehydration, *J. Biol. Chem.* 118: 205-218, 1937.
21. Yannet, H., and Darrow, D. C.: The Effect of Depletion of Extracellular Electrolytes on the Chemical Composition of Skeletal Muscle, Liver, and Cardiac Muscle, *J. Biol. Chem.* 134: 721-737, 1940.
22. Mellors, R. C., Muntwyler, E., and Mantz, F. R.: Electrolyte and Water Exchange Between Skeletal Muscle and Plasma in the Dog Following Acute and Prolonged Extracellular Electrolyte Loss, *J. Biol. Chem.* 144: 773-784, 1942.
23. Trusler, H. M., Egbert, H. L., and Williams, H. S.: Burn Shock; The Question of Water Intoxication as Complicating Factor: Blood Chemical Studies and Report of An Extensive Burn Treated by Repeated Transfusions of Blood and Blood Plasma, *J. A. M. A.* 113: 2207-2213, 1939.
24. Green, H. D., and Bergeron, G. A.: Investigations Regarding the Operation of a Toxic Factor in Ischemic Compression Shock, *Proc. Centr. Soc. Clin. Res.* 17: 60-61, 1944.
25. Allen, F. M.: Theory and Therapy of Shock. Varied Fluid Injections, *Am. J. Surg.* 62: 80-104, 1943.
26. Warren, J. V., Merrill, A. J., and Stead, E. A., Jr.: The Role of the Extracellular Fluid in the Maintenance of a Normal Plasma Volume, *J. Clin. Investigation* 22: 635-641, 1943.

THE ROLE OF INFECTION IN SHOCK PRODUCED BY MUSCLE INJURY*

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THE problem of traumatic shock was first studied intensively during World War I, and the investigations of that period resulted in a clarification of many of its physiologic aspects. These results were summarized in special reports from England,^{1, 2} and in Cannon's³ well-known monograph entitled *Traumatic Shock*. It was believed at that time that the decrease in circulating blood volume was in part a result of toxins elaborated from damaged tissue, which resulted in fluid loss by causing generalized capillary damage. The loss of blood and plasma at the site of injury was not considered adequate to explain the peripheral circulatory failure. The experiments of Blalock⁴ and of Parsons and Phemister⁵ challenged the traumatic toxemia theory and indicated that the local loss of fluid at the site of injury could account for the depletion of the blood volume. Shock research since that time has been primarily concerned with these two mechanisms, but the presence or absence of a traumatic toxin remains unsettled. All agree that the local fluid loss is of utmost importance in the initiation of the shock syndrome, but experimental and clinical evidence supporting the toxic theory is not completely convincing, nor has it been disproved.

Recent work has stressed the importance of infection and the role of bacterial toxins in the pathogenesis of experimental shock. Aub and co-workers^{6, 7} produced shock by muscle tourniquet and found that the sheath fluid resulting produced shock in nine out of thirty-two recipient animals when it was injected intravenously. *Clostridium perfringens* was found in 70 per cent of the traumatized animals, and the toxic fluids were among the most heavily infected. When clostridia were injected into the traumatized muscle, one-half the usual amounts of the resulting fluid produced shock, and the intramuscular injection of *Cl. perfringens* toxin produced local edema followed by a shocklike condition. Although Fine and associates⁸ have presented six reasons why they do not feel that clostridial toxins are necessarily of etiologic significance in tourniquet shock, it does seem reasonable to assume that bacterial toxins do have at least a secondary effect in Aub's experiments. The initial factor of local fluid loss is, however, of primary importance, since bleeding normal dogs a comparable amount produced shock in one-third of the animals.

The experiments of Prinzmetal and co-workers⁹ also emphasize the importance of bacterial contamination of traumatized tissue in the genesis of shock. Quadriceps muscle was removed from the dog's leg under aseptic precautions and replaced, with a shocklike condition resulting in twenty-four hours and death in two to three days. The muscle was always found grossly

This paper was to have been presented at the meeting of the Society of University Surgeons, New York, N. Y., Feb. 8, 1945. (Meeting canceled.)

*This study was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester, School of Medicine and Dentistry.

infected at autopsy, while in other experiments the animals survived with the oral administration of sulfamerazine. The long survival time and the relatively delayed appearance of shock in this type of experiment differentiates it from the more acute process which occurs following muscle crushing (Blalock¹⁰) in the experimental animal, and from the usual type of clinical traumatic shock. It more closely resembles the situation of a grossly contaminated wound which has not had early treatment than the peripheral circulatory failure occurring soon after trauma.

Bacteria of various types commonly occur as inhabitants of normal animal muscle, and Reith¹¹ found 84 per cent positive cultures in the muscles of living hogs, rabbits, and guinea pigs. Gram-positive gas-forming anaerobes are frequently found in dogs' muscle, but it is difficult to rule out the possibility of skin contamination during the biopsy. The dogs' liver usually contains clostridia, and death from the intraperitoneal transplantation of pieces of liver,¹² as well as from bile peritonitis,¹³ can be partially explained on the basis of bacterial infection. It is improbable that clostridia are normal inhabitants of human muscle, but they have been demonstrated in the liver,¹⁴ and are usually present in the intestinal tract. The almost universal contamination of traumatic wounds, especially war wounds, and the high percentage of clostridial contamination makes it necessary to investigate the role of infection in the early phase of shock. The results to be reported indicate that an experimental wound (muscle crushing) may be grossly contaminated with *Staphylococcus aureus* and the shock picture is not altered; contamination with *Streptococcus hemolyticus* and with *Clostridium welchii* shortens the survival period and alters the shock mechanism.

METHODS

Dogs obtained from animal house stock were used in all the experiments, and shock was produced with the Blalock crusher applied to the thigh for five hours at 1,500 pounds pressure, using intravenous nembutal anesthesia. There were five groups of experiments, each including ten or more animals:

1. Control series with the crusher and no infection.
2. Crusher plus infection. Cultures of bacteria were injected into the thigh muscles before application of the crusher as follows:
 - (a) 1 c.c. eighteen-hour broth culture of *Staph. aureus* just before application.
 - (b) 1 c.c. eighteen-hour broth culture of *Staph. aureus* eighteen hours before application.
 - (c) 1 c.c. eighteen-hour broth culture of *Str. hemolyticus* just before application.
 - (d) 1 c.c. eighteen-hour broth culture of *Cl. welchii* just before application.

Following removal of the crusher the animals were observed until death. Arterial blood pressure readings were obtained by direct femoral artery puncture using a mercury manometer, or by means of a carotid artery cannula. In earlier experiments difficulty with contaminated citrate had been encountered, therefore the continuous recording with an arterial cannula has been discarded in favor of repeated arterial puncture. This method is, perhaps, not as accurate, but it obviates the possibility of arterial contamination and the possible effect on the survival time of ligating a carotid artery. Blood volume determinations

were made before application of the crusher and shortly before death of the animal, using the blue dye T-1824 and the spectrophotometer. Blood samples were obtained by arterial puncture to prevent stasis. Plasma proteins were determined by the micro-Kjeldahl method.

Repeated aerobic and anaerobic blood cultures were taken throughout the experiment; the liver and traumatized muscle of the thigh were cultured immediately after death. Citrated blood, 1 c.c., was used to make pour plates for aerobic cultures. Anaerobic cultures were made by inoculating both thioglycolic media and deep meat tubes. A portion of liver and thigh muscle 1 cm. in diameter was removed under aseptic precautions for aerobic and anaerobic study.

OBSERVATIONS

A series of normal animals were infected with the same strains of *Staph. aureus* and *Str. hemolyticus* by injecting eighteen-hour broth cultures into the thigh muscles and were studied as controls. None of these infected animals died. The animals infected with staphylococcus developed abscesses of the thigh, associated with fever and leucocytosis, which localized and ruptured spontaneously. The animals infected with streptococcus developed a diffuse cellulitis of the thigh, had fever and leucocytosis, and appeared quite ill for four to five days. The infection usually subsided without localization and the animals appeared normal in six to ten days. The blood and plasma volumes were followed daily, and they did not show the characteristic changes of shock. The blood pressure remained normal and the blood cultures were negative.

The eighteen-hour Douglas broth deep meat cultures of *Cl. welchii* were obtained from Dr. Andrew Dowdy, and the control observations are taken from his experience.¹⁵ When 1 c.c. of the unfiltered culture is injected into the thigh muscles of a dog, signs of toxicity may develop within three hours, and the leg becomes edematous. General toxicity is marked within six hours, the leg is very edematous, the skin has a bluish-black appearance, and there is a serosanguineous ooze from the skin. Of the control animals, 48 per cent died within twenty-four hours and 12 per cent ultimately survived. A small percentage of the animals died within less than twelve hours.

The typical blood pressure curves of three types of experiments are shown in Fig. 1. There was always a rapid decline in the arterial pressure within one-half hour following removal of the crusher. In the control group there was usually a secondary rise which varied in degree, and in general there was a greater fluctuation in the blood pressure of this group than in the infected animals. The infected animals occasionally had a slight transitory secondary rise, but in most instances the sharp initial decline in blood pressure was followed by a progressive but more gradual fall until death. The swelling of the thigh developed much more rapidly and was much more extensive in the infected animals than in the controls. The rapidity of swelling in the *Cl. welchii* group was startling: within thirty minutes following the removal of the crusher the thigh and adjacent tissues were tremendously edematous.

Survival.—The average survival time following removal of the crusher in twenty control animals was seven hours and twenty-five minutes (Table I). The longest survival time was nine hours and thirty-five minutes, and the shortest was three hours and fifteen minutes. The survival of the animals inoculated with *Staph. aureus* just prior to application of the crusher was approximately the same as the control series. The dogs inoculated with *Staph.*

aureus eighteen hours before crushing survived even longer: an average of nine hours, compared with seven hours and forty-five minutes. The average survival time of ten animals inoculated with *Str. hemolyticus* was five hours and forty minutes; the longest survival was seven hours and fifty-five minutes. The *Cl. welchii* series (ten experiments) had the shortest survival period, which averaged only four hours and thirty minutes, with a minimum

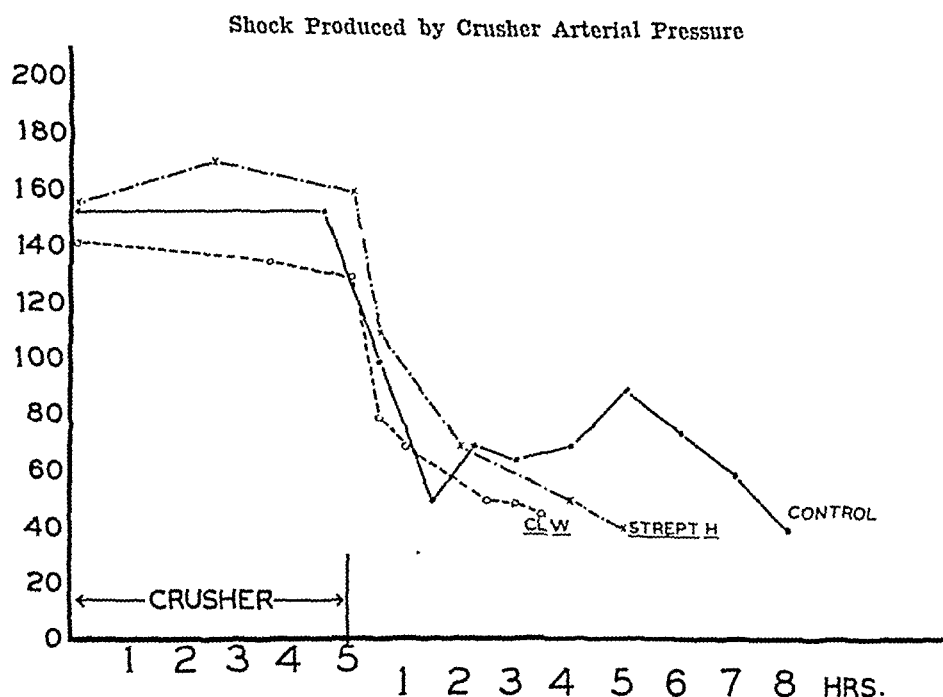


Fig. 1.—Shock produced by crusher arterial pressure.

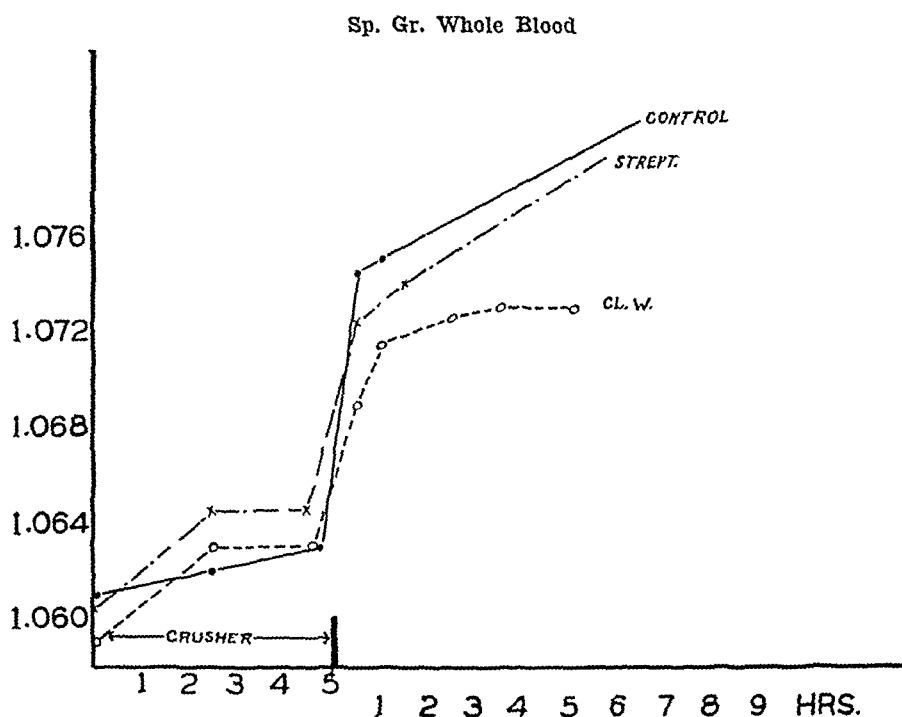


Fig. 2.—Specific gravity of whole blood.

TABLE I. SURVIVAL TIME; SHOCK PRODUCED BY CRUSHING PLUS INFECTION

	AVERAGE HR.	SHORTEST HR.	LONGEST HR.
Control crush	7 hr. 25 min.	3 hr. 15 min.	9 hr. 35 min.
Simultaneous crush and <i>Staph. aureus</i>	7 hr. 45 min.	5 hr. 05 min.	10 hr. 30 min.
<i>Staph. aureus</i> 18 hr. before crush	9 hr.	4 hr. 30 min.	13 hr.
Simultaneous crush and <i>Str. hemolyticus</i>	5 hr. 40 min.	3 hr. 15 min.	7 hr. 55 min.
Simultaneous crush and <i>Cl. welchii</i>	4 hr. 30 min.	2 hr. 55 min.	7 hr. 15 min.

survival of two hours and fifty-five minutes, and a maximum of seven hours and fifteen minutes.

A comparison of blood changes in the control, streptococcus, and *Cl. welchii* groups of experiments is shown graphically in Figs. 2 to 4. The figures represent average figures for each series.

Hematocrit.—The hematocrit in these three types of experiments followed similar trends. It remained quite constant while the crusher was in place, but increased rapidly following its removal. The average total increase in hematocrit in the control series was 23.6 per cent, in the streptococcus series 28.1 per cent, and in the *Cl. welchii*, 27.0 per cent (Table II).

TABLE II. INCREASE IN HEMATOCRIT, WHOLE BLOOD SPECIFIC GRAVITY, AND CONCENTRATION OF CIRCULATING PLASMA PROTEIN

	HEMATOCRIT (%)	SP. GR. OF WHOLE BLOOD (GM.)	CONC. OF CIRC. TOTAL PROTEIN (GM. PER 100 C.G.)
Control crush (20 dogs)	23.6	0.015	0.32
Crush plus <i>Str.</i> (10 dogs)	28.1	0.014	0.53
Crush plus <i>Cl. welchii</i> (10 dogs)	27.0	0.013	0.44

Specific gravity of whole blood (Fig. 2), followed the same pattern in the three groups, but the control animals showed the greatest total change. The whole blood specific gravity of the control animals and animals infected with streptococcus continued increasing after the sharp initial rise, while that of the *Cl. welchii* group tended to remain constant after the first two hours.

The white blood cell count (Fig. 3) increased while the crusher was in place, and decreased during the first hour after removal. A secondary increase then occurred which was maintained until death in the control group, but a secondary fall characterized the infected animals.

The circulating plasma protein concentration (Fig. 4) increased during the application of the crusher and during the first hour after removal. It remained comparatively level in the infected animals, but tended to decrease in the controls before death, and did not return to the normal level. The greatest concentration occurred in the streptococcus series.

The decrease of *plasma volume* and *total circulating protein* was parallel in the three groups, but there were definite variations in the total amount and in the rate of loss. The control animals (Table III) lost 35.4 c.c. of plasma per kilogram and 1.87 Gm. of protein per kilogram. The animals infected with streptococcus had a plasma loss of 26.6 c.c. per kilogram, and the *Cl. welchii* group 27.1 c.c. per kilogram, significantly less than the controls. The rate of plasma loss was about the same in the controls and the animals infected with streptococcus: 4.8 c.c. per kilogram per hour, and 4.7 c.c. per kilogram per

White Blood Cell Count

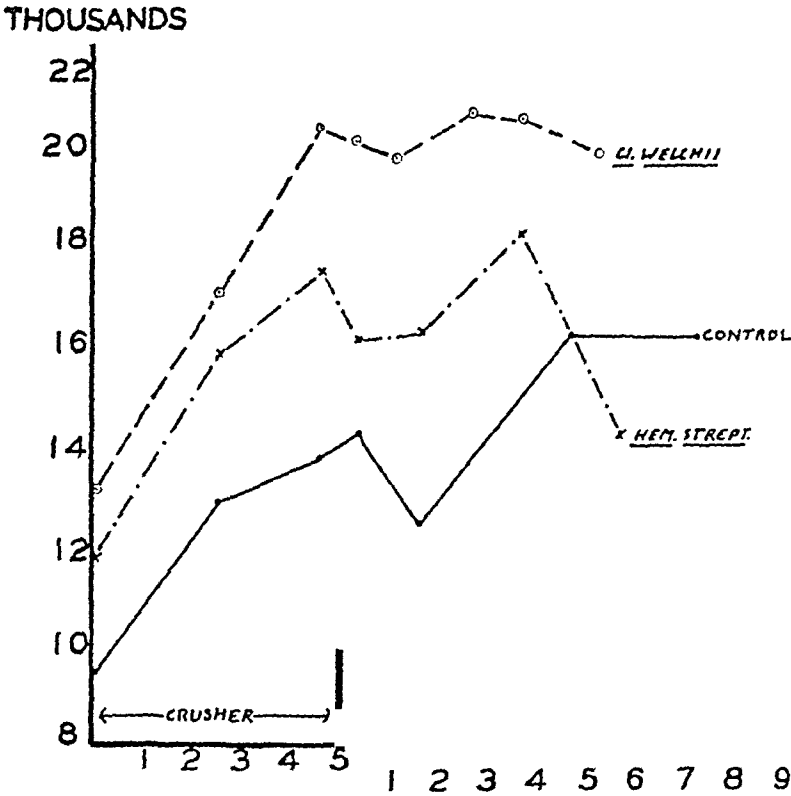


Fig. 3.—White blood cell count.

Total Protein

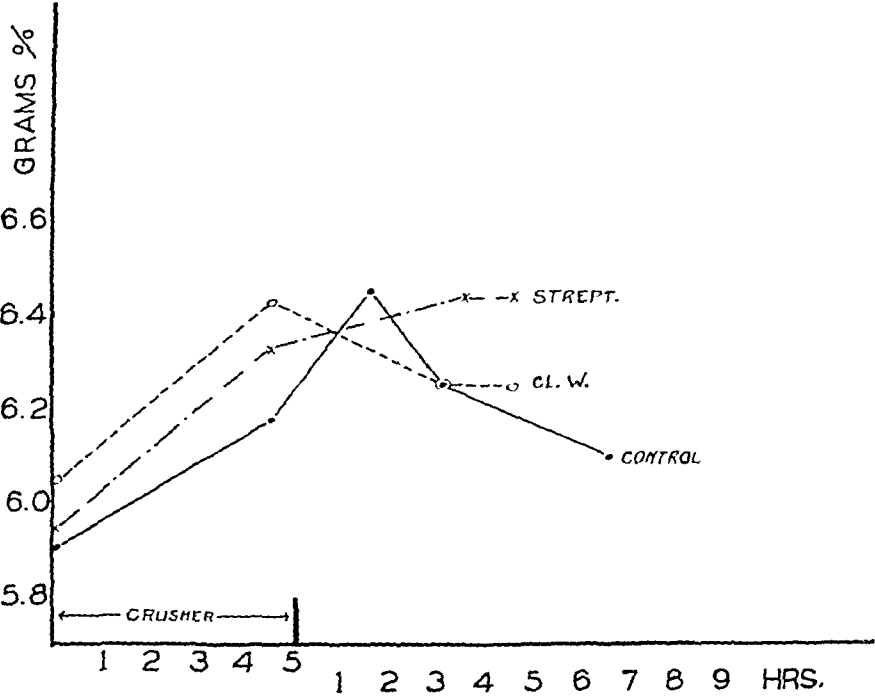


Fig. 4.—Total protein.

TABLE III. PLASMA LOSS IN CONTROL SHOCK COMPARED WITH INFECTION PLUS CRUSH

	PLASMA LOSS (C.C. PER KG.)	CIRC. PROTEIN LOSS (GM. PER KG.)	AVERAGE PLASMA LOSS PER HR. (C.C. PER KG.)	SURVIVAL
Control (20 dogs)	35.4	1.87	4.8	7 hr. 25 min.
Crush plus <i>Str.</i> (10 dogs)	26.6	1.41	4.7	5 hr. 40 min.
Crush plus <i>Cl. welchii</i> (10 dogs)	27.1	1.51	6.0	4 hr. 30 min.

hour, respectively. The animals inoculated with *Cl. welchii* lost plasma at a more rapid rate: 6.0 c.c. per kilogram per hour.

The fluid loss (Table IV) in the traumatized extremity was measured in three series of experiments by comparing the weights of the normal and of the traumatized hindquarters. The blood volume decrease in the controls averaged 34.5 per cent of the normal volume, and approximately 27.8 per cent of the normal was recovered in the traumatized extremity. In the two groups of animals infected with staphylococcus, more fluid could be accounted for in the extremity than the measured loss of blood volume. These measurements, however, include the edema fluid present as the result of infection. The blood volume decrease in shock produced by the crusher compares closely to the amount of blood removed by repeated hemorrhage, which caused death in approximately the same time. The average blood loss which produced death from hemorrhagic shock in five to seven hours was 37 per cent of the circulating blood volume.

TABLE IV. SHOCK PRODUCED BY BLALOCK CRUSHER

	BLOOD VOLUME LOSS IN SHOCK (%)	TOTAL BLOOD VOLUME RECOVERED IN CRUSHED EXTREMITY (%)
Control	34.5	27.8
Simultaneous infection plus crush	32.9	35.0
18-Hr. infection plus crush	31.4	38.6

Average blood volume loss in fatal shock from hemorrhage, 36.9 per cent.

Bacteriology.—

Control animals: Repeated blood cultures during the application of the crusher and after removal showed no bacterial growth except for occasional staphylococcus or streptococcus in the broth, which appeared to be contaminants. Gram-positive gas-forming anaerobes (*Cl. welchii*) were present in the muscle and leg fluid following crush in sixteen out of sixty-three animals, or in 25 per cent. This group did not include dogs that had been inoculated with *Cl. welchii*, but did include animals receiving *Str. hemolyticus*. *Cl. welchii* was found in the liver in 87 per cent of the animals.

Infected animals: The blood cultures were sterile in the *Str. hemolyticus* series both during application of the crusher and after removal. Terminal blood cultures were also sterile. A positive culture was encountered in one animal after removal of the crusher, but at autopsy an acute cystitis was found, and cultures of the bladder showed streptococcus. Inasmuch as it may appear unusual that so many dogs had negative blood cultures, it should be noted that cultures were taken prior to the day of the experiment, and animals with bacteremia were discarded. *Str. hemolyticus* was, of course, always present in the leg fluid and *Cl. welchii* was present in the leg muscle of two animals.

The blood cultures in the *Cl. welchii* series were frequently positive, and since there did not seem to be any definite pattern in relation to the crusher, the results are tabulated in Table V. *Cl. welchii* was always isolated from the leg fluid and liver.

TABLE V. BLOOD, LEG MUSCLE, AND LIVER CULTURES IN *CL. WELCHII* PLUS CRUSH

DOG NO.	CONTROL CULTURE	DURING CRUSH	JUST PRIOR TO RELEASE	15 MIN. AFTER RELEASE	2 HR.	2 TO 4 HR.	LEG FLUID OR MUSCLE	LIVER
43-398		-	-	-	-	-	+	+
43-387	-	-	-	-	-	-	+	+
43-408	-	-	-	-	-	+	+	Str.
43-373						-	+	+
43-372	-	+	-	-	+	-	Staph.	Staph.
43-314				-	-	-	+	+
43-424	-		-	-	+	-	+	+
43-417	-	-	-	Str.	-	-	+	Str.
43-411		-	+	-	-	-	+	+
43-414			-	-	-	-	+	-
43-344		-	-	+	-	-	+	+
43-265	-	-	-	-	-	-	+	Staph.

+, *Cl. welchii*

-, Negative culture

Pathology.—The animals were autopsied immediately following death, and portions of the organs saved for microscopic study. The changes noted were as follows:

Heart: The heart was usually dilated. The muscle showed no gross or microscopic abnormality other than occasional fragmentation. This fragmentation was not constantly present, but occurred most frequently in animals infected with *Cl. welchii*.

Lungs: Basilar congestion was present, but the lungs were not generally congested or edematous.

Liver: The liver appeared congested and swollen. On microscopic examination there was marked central congestion. The liver cells appeared frothy and were vacuolated, indicating cloudy swelling and probably fatty degeneration. This change was most marked in the central area, and focal necrosis was occasionally present. The appearance of the liver was essentially the same in all the animals, although the changes in the clostridial group seemed more marked than in the control and streptococcus series.

Spleen: The spleen was contracted and frequently contained hemorrhagic infarcts.

Gastrointestinal tract: The stomach appeared normal. The duodenum showed mucosal congestion and occasional actual hemorrhage with superficial ulceration. This change was similar in the three groups of experiments. The jejunal mucosa was also occasionally congested in the proximal portion, and in many animals bloody fluid was present in the lumen.

Adrenal: The adrenals appeared normal in most instances, but hemorrhage in the medulla was occasionally seen.

Kidneys: The kidneys were grossly congested and swollen. Microscopically there was always marked capillary congestion and extensive cloudy swelling of the tubular epithelium; the lumen of the tubule was often filled with cellular debris. Pink-staining amorphous precipitate was present in the glomeruli, but no definite necrosis was noted. Casts were present in the collecting tubules.

Traumatized muscle: The muscle of the control animals at the time of death was very edematous and macerated, and bloody fluid oozed from the cut section. Microscopically, there were fragmentation of the muscle bundles, edema, and hemorrhage. The streptococcus series showed the same change except for more prominent edema and some leucocytic infiltration. The muscle of the animals inoculated with *Cl. welchii* showed much more marked changes. Pockets of gas were present, and the muscle had a bluish-black gangrenous appearance. The edema fluid was dark and frothy and on cut section the muscle was soft, necrotic, and amorphous. The local evidence of gas gangrene was confined to the area of the thigh which had been crushed and had not spread to the normal muscle or to the trunk of the animal.

DISCUSSION OF RESULTS

The shock or peripheral circulatory failure which follows the removal of the crusher is quite similar to that seen following experimental intestinal trauma, tourniquet shock, and muscle trauma produced by other methods. The rather precipitous drop in blood pressure following removal of the crusher is more striking than is seen following intestinal trauma or muscle injury of other types. There is marked hemoconcentration, an increase in the whole blood specific gravity, and increased blood viscosity, and the concentration of circulating plasma protein increases slightly. The circulating (measurable) plasma and whole blood volumes decrease. Following the removal of the crusher the injured thigh becomes enormously swollen, and at autopsy bloody fluid oozes from the muscle. This fluid contains less protein than normal plasma and less hemoglobin than whole blood. All of the leg fluids and traumatized muscle were cultured both aerobically and anaerobically, and *Cl. welchii* was isolated in 25 per cent. Many of the leg fluids and muscle showed no growth on either aerobic or anaerobic culture.

The amount of fluid lost in the traumatized extremity is nearly equal to the measured loss of blood volume. This again emphasizes the importance of local fluid loss as an initiating factor in shock, and is an excellent argument against the hypothesis that there is a generalized capillary permeability and general fluid loss in shock.

The infected animals differed from the controls especially in survival time, which is two hours shorter with streptococcus infection, and three hours shorter with *Cl. welchii*. The blood pressure curves show the same prompt initial fall, but the infected animals do not have the secondary rise in arterial pressure that is present in the controls. There are differences in the whole blood specific gravity and in the white blood count, as previously noted, but the changes are of minor importance. The swelling of the thigh is more marked with the streptococcus than in the controls, but *Cl. welchii* is associated with the greatest edema; swelling becomes maximal within thirty minutes, the leg is bluish, and crepitation is present before death. In spite of the tremendous swelling, the plasma loss from the circulation in the infected animals is less than in the controls. The controls lose an average of 35.4 c.c. of plasma per kilogram, while the infected animals lose 26.6 and 27.1 c.c. of plasma per kilogram. The rate of plasma loss is the same in the controls and with streptococcus, but is more rapid in the *Cl. welchii* group.

There are many possible reasons why the survival period of animals infected with streptococcus and *Cl. welchii* is shorter than that of the controls

or those infected with staphylococcus, but the factors of local fluid loss and of circulating bacterial toxins deserve the most serious consideration. It can be argued that the infected animals have a greater initial fluid loss at the site of trauma with a more rapid initial blood volume depletion. The group infected with staphylococcus did lose more fluid at the site of trauma than the controls, but their survival time was not decreased. The animals infected with streptococcus and *Cl. welchii* did not have as great a decrease in the plasma volumes at the time of death as did the controls. It would follow from these observations that the differences in survival cannot be explained on the basis of greater local fluid loss, and that there is a systemic effect of the bacterial infection (bacterial toxin) which is added. The difference in the blood pressure curves suggests, however, a possible difference in the physiologic response of the infected animals. The secondary blood pressure rise seen in the control animals is usually explained on the basis of vasoconstriction, a narrowing of the circulatory bed to compensate for the decreasing blood volume. The absence of the secondary rise with streptococcus and *Cl. welchii* suggests that the infection may deprive the animal of this compensatory mechanism.

The experiments of Aub and his co-workers^{6, 7} have led them to believe that in experimental shock (especially tourniquet shock) the much sought after "toxin" is probably bacterial in origin and primarily the toxin of clostridia. This may also be true in shock resulting from muscle trauma with the crusher, but there are several characteristics of the control experiments which are not in complete accord with this hypothesis.

In these experiments *Cl. welchii* was found in the muscle in only 25 per cent of the animals (not inoculated with clostridia), and these animals did not have the shortest survival times. The deliberate inoculation of the muscle with clostridia prior to crushing shortened the survival time and modified the course of the shock.

The pathologic lesions found in animals dying of shock are in some respects similar, but in others definitely different from those present in fatal clostridial infection. The central congestion, fatty degeneration, and focal necrosis of the liver are commonly found in both conditions. The muscle fragmentation is seen after removal of the crusher, but this can as well be a mechanical as a toxic effect. The duodenal hemorrhage, the kidney lesions, and the adrenal hemorrhages were not seen by Favata and associates¹⁶ in their dogs which died from clostridial infection or injection of their toxins. These lesions are usually present in experimental traumatic shock. In discussing tourniquet shock, Fine, Frank, and Seligman⁸ state that, "The death from tourniquet shock is extraordinarily rapid, a matter of a few hours usually, following release of the tourniquet, so that too little time is available for development of enough toxin to be the lethal agent." This short duration certainly does not preclude the development of enough toxin to cause damage to the animal, as many of Dowdy's animals were toxic within three hours after intramuscular injection of the cultures. The amount of toxin which can be formed within a relatively short time, added to the fluid loss, can well be a potent factor in causing the animal's death. However, more experimental evidence must be obtained before we conclude that bacterial toxins are always a factor in rapidly developing experimental shock due to muscle injury or muscle ischemia. It is noteworthy that bacteremia was not encountered in the streptococcus experiments, and only occasionally with clostridial infection.

The decrease in the survival time following injury to muscle inoculated with *Str. hemolyticus* and with *Cl. welchii*, as compared with the control animals and those inoculated with staphylococcus, emphasizes the important role which wound contamination may have in traumatic shock. The importance of wound infection is so obvious that comment is unnecessary, but these observations indicate that simple wound contamination may profoundly affect the shock resulting from injury.

CONCLUSIONS

Shock has been produced in dogs by means of the Blalock crusher. The inoculation of virulent cultures of *Str. hemolyticus* and *Cl. welchii* into the thigh muscles just before application of the crusher modifies the resulting shock. The survival time of animals inoculated with *Str. hemolyticus* is two hours less than the control animals, and those inoculated with *Cl. welchii* survive three hours less than the controls. *Staph. aureus* injected into the thigh muscles before injury does not alter the survival time under the conditions of these experiments.

There is no greater fluid loss in the infected animals than in the controls, and the decreased survival time is considered to be due to the infection of traumatized muscle and to circulating bacterial toxins. The infected animals do not have a secondary rise in blood pressure following the primary fall.

REFERENCES

1. Medical Research Committee, Special Report Series, No. 25, Reports of the Special Investigation Committee on Surgical Shock and Allied Conditions: Wound Shock and Haemorrhage, London, 1919, His Majesty's Stationery Office, pp. 285.
2. Medical Research Committee, Special Report Series, No. 26, Reports of the Special Investigation Committee on Surgical Shock and Allied Conditions: Traumatic Toxaemia as a Factor in Shock, London, 1919, His Majesty's Stationery Office, pp. 47.
3. Cannon, W. B.: Traumatic Shock, New York, 1923, D. Appleton-Century Company, Inc., pp. 201.
4. Blalock, Alfred: Experimental Shock: Cause of Low Blood Pressure Produced by Muscle Injury, Arch. Surg. 20: 959, 1930.
5. Parsons, E., and Phemister, D. B.: Hemorrhage and Shock in Traumatized Limbs: Experimental Study, Surg., Gynec. & Obst. 51: 196, 1930.
6. Aub, Joseph C., Brues, Austin M., Du Bois, Rene, Kety, Seymour S., Nathanson, Ira T., Pope, Alfred, and Zamecnik, Paul C.: Bacteria and the "Toxic Factor" in Shock, War Med. 5: 71, 1944.
7. Aub, Joseph C.: A Toxic Factor in Experimental Traumatic Shock, New England J. Med. 231: 71, 1944.
8. Fine, Jacob, Frank, Howard A., and Seligman, Arnold M.: Traumatic Shock; VIII. Studies on the Therapy and Hemodynamics of Tourniquet Shock, J. Clin. Investigation 23: 731, 1944.
9. Prinzmetal, M., Freed, S. C., and Kruger, H. E.: Pathogenesis and Treatment of Shock Resulting From Crushing of Muscle, War Med. 5: 74, 1944.
10. Blalock, Alfred: The Uniform Production of Experimental Shock by Crush Injury: Possible Relationship to Clinical Crush Syndrome, Ann. Surg. 115: 684, 1942.
11. Reith, Allan: Bacteria in the Muscular Tissues and Blood of Apparently Normal Animals, J. Bact. 12: 367, 1926.
12. Abraham, E. P., Brown, G. M., Chain, E., Florey, H. W., Gardner, A. D., and Sanders, A. G.: Tissue Autolysis and Shock, Quart. J. Exper. Physiol. 31: 79, 1941.
13. Harkins, Henry N., Harmon, Paul H., and Hudson, Jeanne E.: Peritonitis Due to Bile and to Liver Autolysis, J. A. M. A. 107: 948, 1936.
14. Mason, E. C., and Hart, M. S.: Welch-Like Bacillus in Human Liver, J. Lab. & Clin. Med. 25: 835, 1940.
15. Dowdy, Andrew H., Sewell, R. L., and Vincent, J.: The Prophylaxis and Therapeutics of Clostridium Infections (Gas Gangrene), New York State J. Med. 44: 1890, 1944.
16. Favata, B. V., Dowdy, A. H., Sewell, R. L., and Vincent, J. G.: The Pathology of Experimental Clostridial Infections in Dogs, Surg., Gynec. & Obst. 79: 660, 1944.

HYDRONEPHROSIS

I. THE STRUCTURAL CHANGES

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THE structure of the kidney is intricate and our present knowledge of parts and components has been achieved through years of study by many men. Such names as Bowman, Malpighi, Henle, and Schweigger-Seidel are symbolic and others, Peter, Huber, Traut, etc., are classical in this field. Although renal structure is now well known, opinions on certain structural relations still differ. There is no fast agreement on the structural unit and its correlation with the functional unit, on the renal lobule (or pseudolobule), on nutrient arteries, end arteries, or arteriolae rectae spuriae. (Is all blood to the tubules postglomerular?) Strangely enough, the tubular structure of the kidney has been studied over all these years by means of just two methods, reconstructions and teased dissections. During this period such men as Cohnheim, Ponfick, Suzuki, Fabian, Strong, Clark Johnson, and others have studied the tubular changes of hydronephrosis by the same two methods. Unfortunately, neither method demonstrates satisfactorily the later changes of hydronephrosis and, consequently, there is much room for differences of opinion. Investigators interpret differently the discoveries made by the same method. Two recent contributions from the findings of the maceration-dissection method illustrate this point. Many questions may have to remain unanswered unless a newer, more accurate method of demonstrating the changes than either of these two is discovered.

The outer and inner changes of hydronephrosis are familiar to every student of pathology. Outwardly, the whole kidney looks engorged and cystic. It is tense and distended. It is obviously overfilled. On section, the pelvis collapses and, with the escape of its fluid contents, all that is left of its inner surface is a shell of parenchyma showing corrugations, the umbrella-like ribs of which conform to the particular type of vascular tree of the species of animal (Fig. 1). In the past, descriptions have been largely of the changes occurring after complete ureteral obstruction in experimental animals, and have been confined a little too closely to tubular changes. Nevertheless these studies are useful since the changes in animals no doubt are similar to those occurring with partial obstruction of the human kidney. The unipolar kidney (rat, guinea pig, rabbit, cat, dog, sheep, and whale), however, is structurally different from the multipolar kidney (cow, monkey, pig, seal, and man). Many of these kidneys also have their own tubular peculiarities. For example, the Henle loop in seals is short and in rabbits, long. The venous circulation of the cat is unique, totally different from all the others, and the changes of hydronephrosis in cats differ from the others in the absence of the usual progressive enlargement (Fig. 2). Birds, reptiles, amphibia, and fish have apeliac mesonephroi without papillae. They show tubular dilatation and atrophy, it is true, but of a kind as different as their structure. The aglomerular kidneys of Teleostomi probably would not become hydronephrotic at all because basically hydronephrosis is glomerular.



Fig. 1.



Fig. 3.

Fig. 1.—Photograph of the inner cut surface after sagittal section of an advanced hydronephrosis from a ureteropelvic partial obstruction. Note the intrarenal type of pyelectasis, the calical cavities and the varying thicknesses of the parenchymal rim. The inside ribs are formed of larger blood vessels which are resistant to backpressure and the best preserved parenchyma is that with the least anemic atrophy. The whole parenchymal area nevertheless still shows functioning glomerulo-tubules. (See photomicrographs from areas I, II and III reproduced in Figs. 4, 6 and 7.) (This human specimen is most unusual in the absence of all infection and of all evidence that there ever has been any.)

Fig. 3.—The corticomedullary line demonstrated by arterial injection of barium sulfate in complete ureteral obstruction, seven days in duration, of a unipapillary sheep's kidney. Note the compression of interlobar and arcuate veins by pelvic distention. (From Hinman F.: Surg., Gynec. & Obst. 58: 356, 1934.)



Fig. 2.—Intrarenal type of hydronephrotic atrophy in the cat. A, Complete obstruction of the ureter for thirty-eight days shows a similar degree of hydronephrotic atrophy but without the gross enlargement as in other animals. B, The peculiar external arrangement of the veins on the surface act as an oncometer, preventing much enlargement.

The changes in a rabbit cannot be accepted, therefore, as gospel for man or other animals.

Traumatic is the word for the early changes of hydronephrosis. The surface of the kidney looks edematous and hemorrhagic. On section, engorgement marks the corticomedullary line and bloodstreaks radiate from that line outward into the cortex and inward toward the papilla (Fig. 3). The mushy papilla early shows superficial splits, later torn excavations, and after several days it flattens out and disappears. These traumatic changes characterize early stages; later, the epithelial surface of the dilating pelvis becomes intact, the continuity of the pelvic epithelium with that of collecting ducts having been restored. Pelvic tears are no longer seen. During the first few days the pelvic content, usually blood tinged, gradually increases in amount up to fifty or sixty days (rabbit), after which it diminishes and the renal weight parallels these changes (Table I). The rim of renal parenchyma grows thinner as dilatation progresses but retains its corticomedullary distinction almost up to ultimate destruction (Fig. 4).

TABLE I. RELATION OF FLUID VOLUME TO RENAL WEIGHT IN PROGRESSIVE HYDRONEPHROSIS

Duration of obstruction (days)*	1	3	6	10	14	21	28	36	46	61	90	114	163	231
Volume of pelvic fluid (in cubic centimeters)*	4	6	8	9.6	10	12	18.4	35	46	40	15	12	10	6
Approximate weight of the hydronephrotic kidney†	100	110		150		170		180		100			80	60

*From Strong, Kenneth C.: Arch. Path. 29: 78, 1940.

†After Ponfick: Beitr. z. path. Anat. u. z. allg. Path. 40: 127, 1910.

The tubular changes are hard to follow microscopically because the ability to distinguish different components of the unit is soon lost and therefore reconstructions which can be made of the early stages are impossible in later ones. Dilated, collapsed, and atrophied parts of a tubule soon look alike and proximal or distal convolutions, ascending or descending limbs, connecting or collecting ducts become indistinguishable. Glomeruli remain longest, many in good preservation, but what has happened to their individual tubules has long been a matter of conjecture. Some proximal convolutions and Henle's loops also survive, apparently as scattered remnants in a mass of atrophy. Are these tubular components and these glomeruli still functioning as units or have certain parts of a tubule as well as its own and other glomeruli each become independent? After all, the tubule is not the whole of renal structure nor is it the essence of renal function, or even the unit of either. It takes a group of glomerulotubules to form such a unit (Fig. 5) and this is locked inseparably with blood supply. In understanding the pathogenesis of hydronephrosis, therefore, the vascular changes are no less important than the tubular. Finally, what is the effect on function of these progressive changes of hydronephrosis? Comparing the microscopic sections of two kidneys, grossly appearing to have about equal degrees of hydronephrotic atrophy, one caused by complete and the other by partial obstruction, so similar are the changes that it is not possible to distinguish between them. The kidney only partially blocked certainly has been functioning all the time, even if less and less efficiently. Why would the kidney totally blocked not have had to be functioning all the time also and, if not, why are the pathologic

changes so exactly the same? All of these progressive changes—phylogenetic, tubular, arterial, venous, and functional—are certainly interrelated and together can give some inkling of what goes on in a kidney with a blocked ureter. Even with the exercise of a good imagination, conclusions from a study of tubular changes alone are incomplete, just as is Suzuki's division of the progressive changes seen on microscopic studies with indigo carmine intravitaly, into the three stages of (1) general dilatation, (2) beginning collapse of "Hauptstücke and Schleifenshenkel," and (3) terminal collapse of collecting ducts.

Tubular Changes.—The ultimate subdivision of renal structure leaves a glomerulus and its tubule. They are indivisible although Oliver suspects, from having discovered aglomerular tubules and atubular glomeruli in his dissections, that these glomerular and tubular components do function independently. The single glomerulo-tubule, however, is not a complete functional unit but must be grouped with others of its kind in order to function normally. The first effect

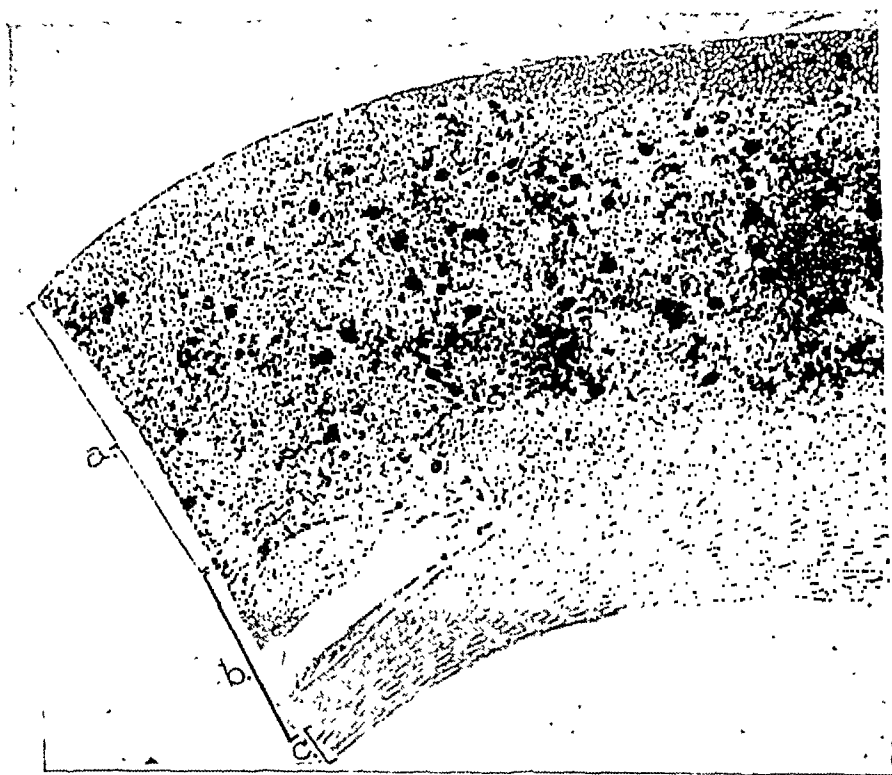
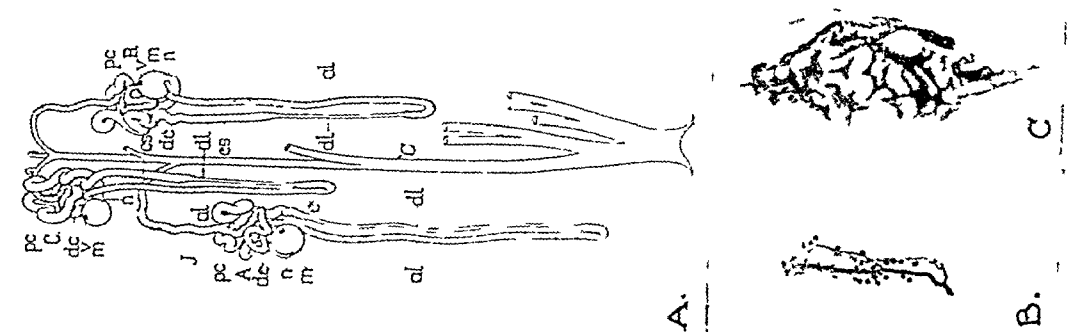
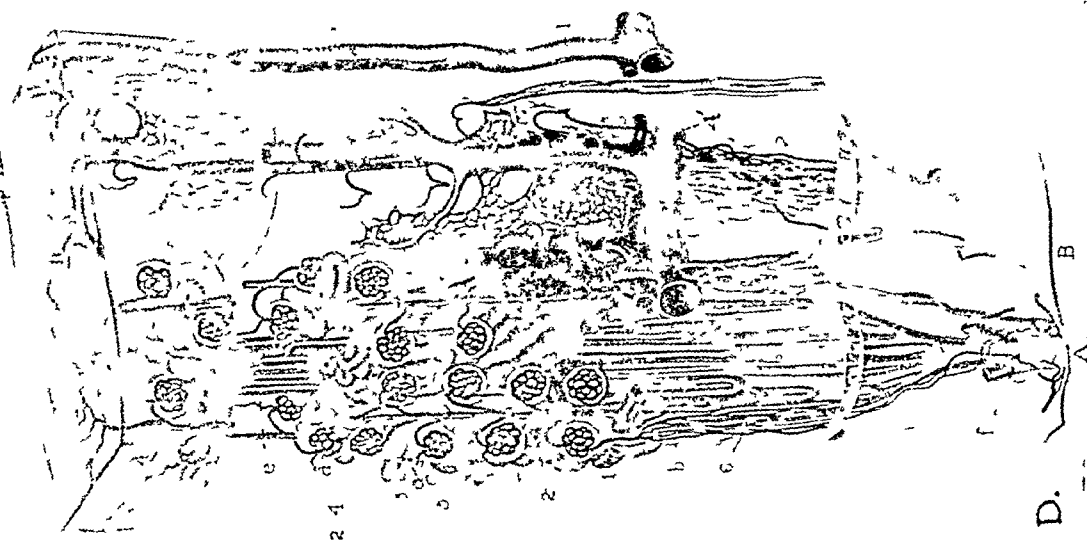
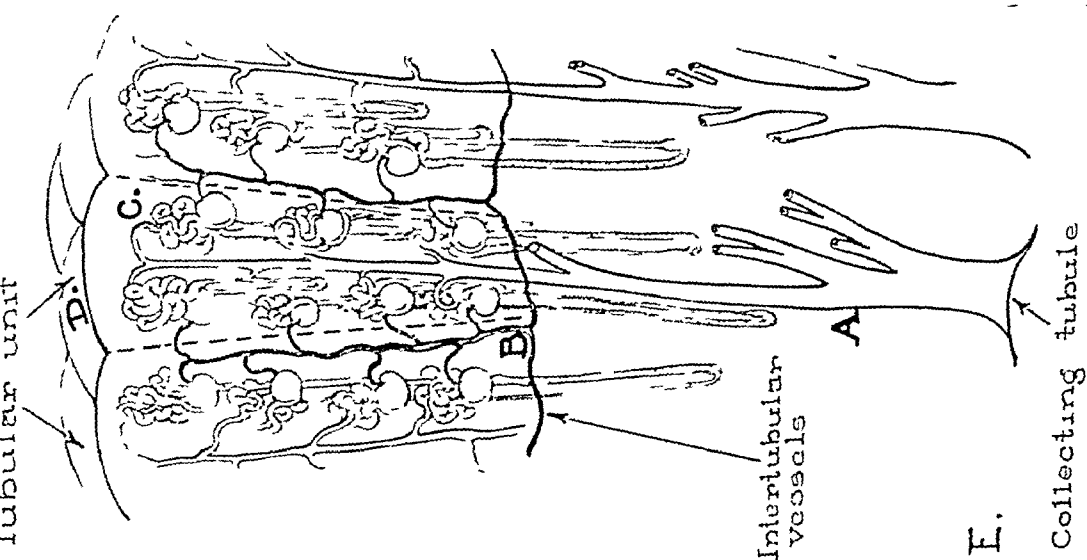


Fig. 4.—Tubular changes. Photomicrograph of the area I of the hydronephrotic kidney shown in Fig. 1. Note the more or less uniform dilatation of the tubules with fairly good preservation of a rule be identified, (a) proximal and distal dilatation caused as are indistinguishable as collecting tubules. In the middle, the loops of the collecting system which they parallel (b). The te ducts are the most dilated of all and their elongation is indicate usually either obliquely or longitudinally (c) rather than straight across (as the tubules in b). This picture demonstrates the difficulty of interpreting the later tubular changes correctly from microscopic and camera lucida reconstructions. There are no longitudinal rays of tubules in the cortex as seen in thicker parts of the parenchyma (see Figs. 6 and 7).

of back pressure on the tubule is dilatation, most marked in the collecting ducts, but more or less general in all tubular components in all poles and regions (Fig. 6). Soon the epithelium which lines some dilated ducts shows flattening and that which lines other collapsed ducts alongside shows atrophy. With atrophy comes replacement with leucocytes and connective tissue until, finally, interstitial fibrosis replaces almost all tubular structures. Right to the end closely packed glomeruli persist in compressed areas with little if any fibrosis or hyaline change (Fig. 7). With them are cystic collecting tubules whose connection, if any,

tubular unit



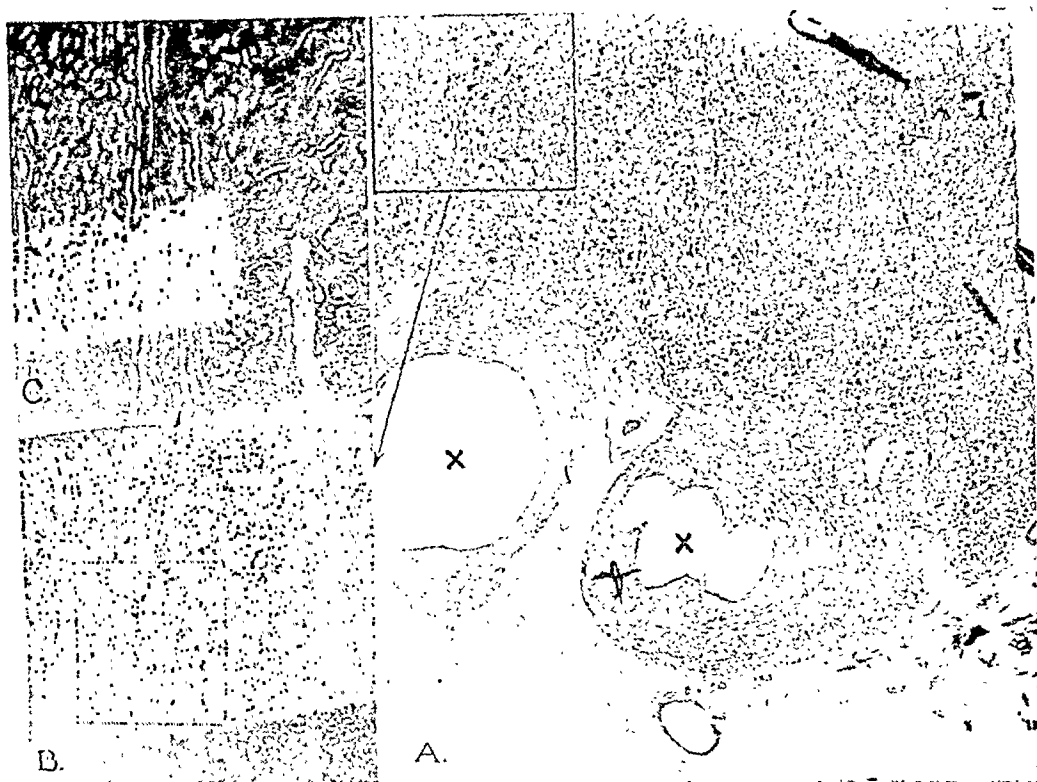


Fig. 6.—Photomicrograph from area II of Fig. 1. The upper limits of two calical cavities (X) show closely packed collecting ducts encircling and entering them. The rays of longitudinal tubules throughout the parenchyma are tubular cores of structural units (Fig. 5). In B and C, glomeruli and tubules to the left of the core of collecting ducts are much more atrophic than those to the right. The encircling glomeruli of this particular unit group of tubules get blood from different interlobular arteries lining the circumference of the cylinder and those at the left in B and C have been pinched or compressed more than those at the right.

Fig. 5.—Renal structure.

A, Reconstruction of three glomerulotubular units, a structural but not a functional unit. (A) Diagram of a tubule, the renal corpuscle of which is situated in the lowermost portion of the cortex; (B) about the middle of the cortex; (C) in the outer portion of the cortex. (m) Renal (malpighian) corpuscle; (v) vessel porta, (n) neck; (pc) proximal convoluted portion; (es) medullary segment, (dl) descending limb, (al) ascending limb of medullary loop (loop of Henle), (dc) distal convoluted portion, (j) junctional tubule (c) collecting tubule. (From Huber, G. Carl: The Harvey Lectures, 1909-10, pp. 120.)

B, Photomicrograph of collodion cast of two interlobular arteries with glomeruli.

C, Photomicrograph of a glomerulo-tubule isolated by the method of maceration and needle dissection (Henle's loop is missing). (From Oliver, J., and Lund, E.: Arch. Path. 15: 755, 1933.)

D, Model drawing of the vascular-tubular relationship with a cylindrical group of glomerulo-tubules packed around the core of their collecting ducts roughly in the form of a pyramid with the glomeruli surrounding it peripherally. (A) The central tubular arrangement with peripheral circulation, forming a cylinder-like unit. Tubular arrangement shows (a) proximal convoluted portion, (b) loop portion, (c) distal convolution in neighborhood of proximal, (d) the connecting piece, (e) the collecting duct, emptying into (f) the common duct of Bellini on the renal papilla. The arterial tree is shown as (1) the interlobar or arcuate, (2) the interlobular, (3) the afferent glomerular, (4) glomeruli arranged in circular manner about the tubular core, (5) the efferent glomerular, and (6) the arteriae rectae. (B) represents the unit without the tubular system drawn in, showing the venous tree. (1') The plexus of collecting veins, (2') the venae rectae which is also a plexus, (3') the interlobular veins, and (4') the arcuate and interlobar veins. (From Hinman, F.: Principles and Practice of Urology, Philadelphia, 1935, W. B. Saunders Company.) (See Fig. 6.)

E, Model sketch of a functional unit conceived as a tree with its trunk the collecting duct with neighboring ones in outline. The unit is reconstructed from the accompanying illustrations: (A) The collecting tree, (B) the interlobular arteries with their glomeruli, (C) a compact glomerulo-tubule (Henle's loop not shown), (D) the vascular-tubule relationship. The unit is a cylindrico-pyramided group of glomerulo-tubules emptying into one collecting duct which branches out into the group dichotomously like a tree to its fruit. The group is a unit, however, only with reference to a duct in common. The blood supply comes in at the periphery from many different interlobular arteries which also supply glomeruli of neighboring cylindrico-pyramidal groups of tubules. It is obvious that the effects of obstruction of the collecting duct might be more or less uniform but that the effects of anemia in the group might vary enormously if some interlobular arteries were unaffected and others constricted.

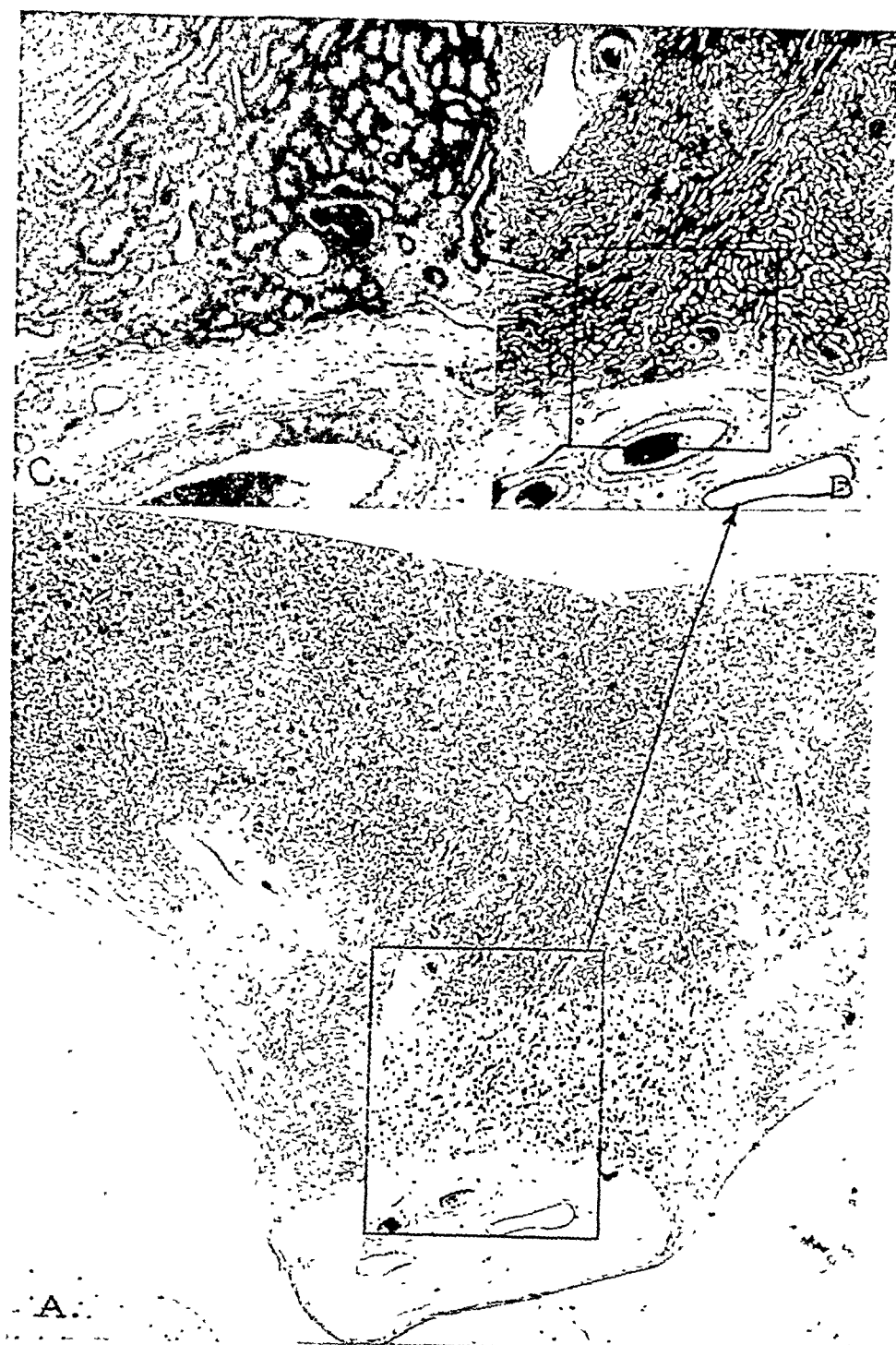


Fig. 7.—Photomicrographs from area III, Fig. 1. Glomeruli are scattered and fewer in number. Tubular atrophy and replacement by connective tissue are clearly seen even in the low-power magnification (A). The foreshortening and tortuosity with atrophy are shown in B and fibrosis is pronounced in the lower portion of C.

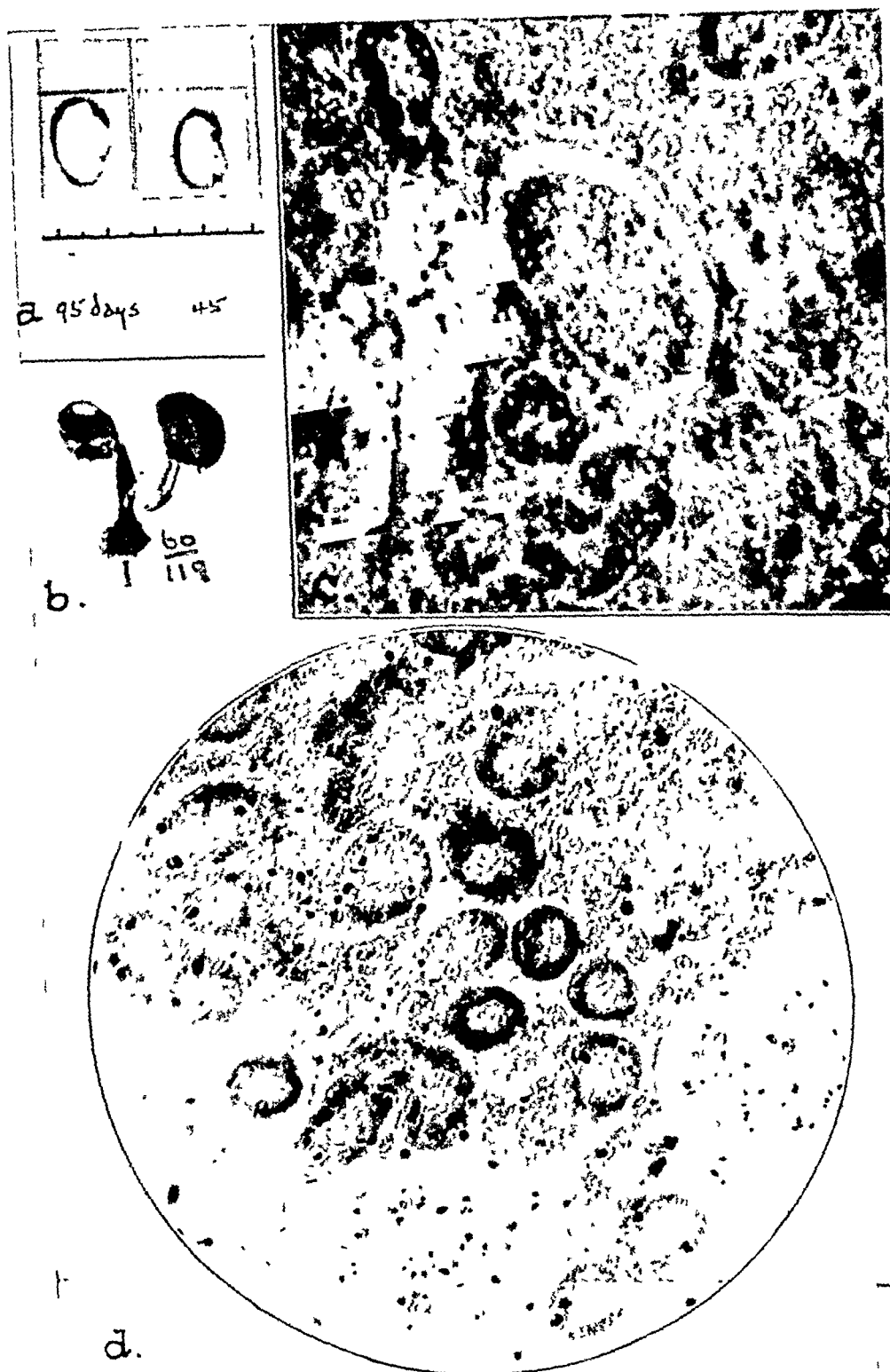


Fig 8.—Repair of hydronephrosis in the rat. *a*, Sagittal section of two entire kidneys after complete ureteral obstruction lasting ninety-five and forty-five days, respectively. The rim of parenchyma is very thin. *b*, The repair kidney and its hypertrophic mate 119 days after relief of a complete ureteral obstruction sixty days in duration. There is one repair nodule in the central zone which stands out lighter in color in the photograph because of the intravital stain. This nodule, however, would not maintain life after removal of the opposite kidney. *c*, Photomicrograph (high power) of a portion of the repair nodule (*b*). The intravital stain is deepest in convoluted tubules which are seen to be hypertrophied when compared with a similar section of a normal kidney, shown in *d*. (*a*, *b* and *c* from Hinman, F. Tr. Sect. Genito-Urin Dis., A. M. A. pp. 103-117, 1918, *d*, from Hinman, F. Tr. Am. A. Genito-Urin Surgeons 15: 259, 1922.)

with these glomeruli has remained unsolved until just recently partially disclosed by actual dissection. The foregoing changes are progressive, but not uniformly so, throughout the kidney. The renal portions showing slowest progress in hydronephrotic atrophy differ with species. The glomerulo-tubules of either one or both poles function longest in dogs, those of the central area, longest in rats and rabbits (Fig. 8). In man, the renal portions relatively less

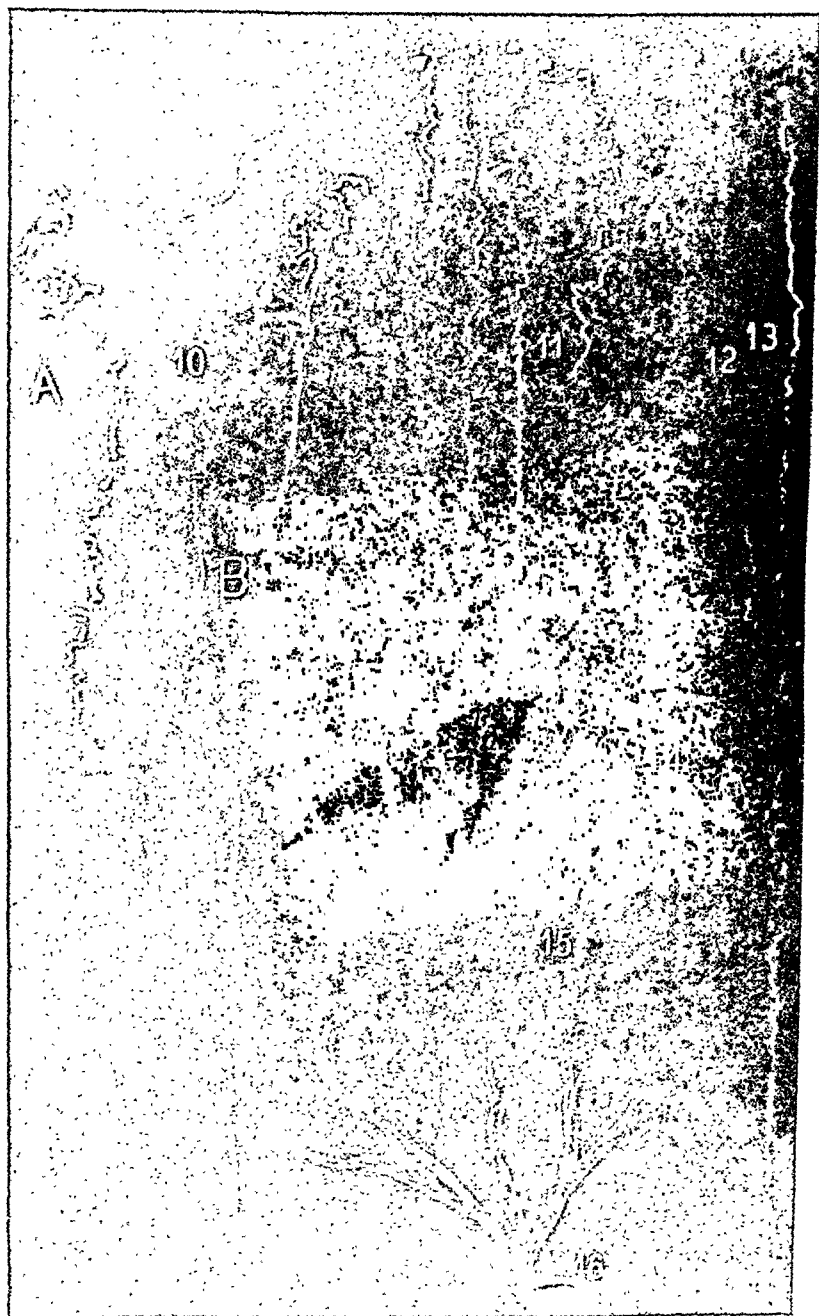


Fig. 9.—Glomerulo-tubular units isolated by the method of maceration and microscopic dissection. (10) A normal glomerulo-tubule (A) and its collecting duct tree (B). (A) The usual grouping together of proximal and distal convolutions has been split by dissection (see Fig. 13). (B) The collecting duct shows division to the seventh degree; note its length. (11) Proximal convolutions unraveled from the central portion after six days' obstruction show atrophy which, after fourteen days, has become marked in the lateral portion (12), but is slight in the intermediate portion (13) after twenty-one days (see Fig. 10); one convolution from the intermediate portion (14) is even well preserved after twenty-eight days. In (15) is a convolution three days after obstruction and in (16) are normal isolated ducts of Belini. (From Strong, Kenneth C.: Arch. Path. 29: 77, 1940.)

affected by hydronephrotic atrophy vary largely, as will be shown, according to the circulatory arrangement, the slowest progress of atrophy being where blood vessels are the least compressed by tubular and pelvic dilatations. Pressure atrophy is more or less uniform throughout the kidney but anemic atrophy is not. This variation in the rate of tubular atrophy in different renal portions is seen microscopically (see Figs. 6 and 7) and is demonstrable by dissection (Figs. 9 and 10). Just what happens when all portions of a tubule have atrophied can only be surmised. Do glomeruli retain a duct through which their filtrates can drain directly into the pelvis, as stated by Fuchs from induction and demonstrated by Johnson (Fig. 11), or are they completely isolated as interpreted by

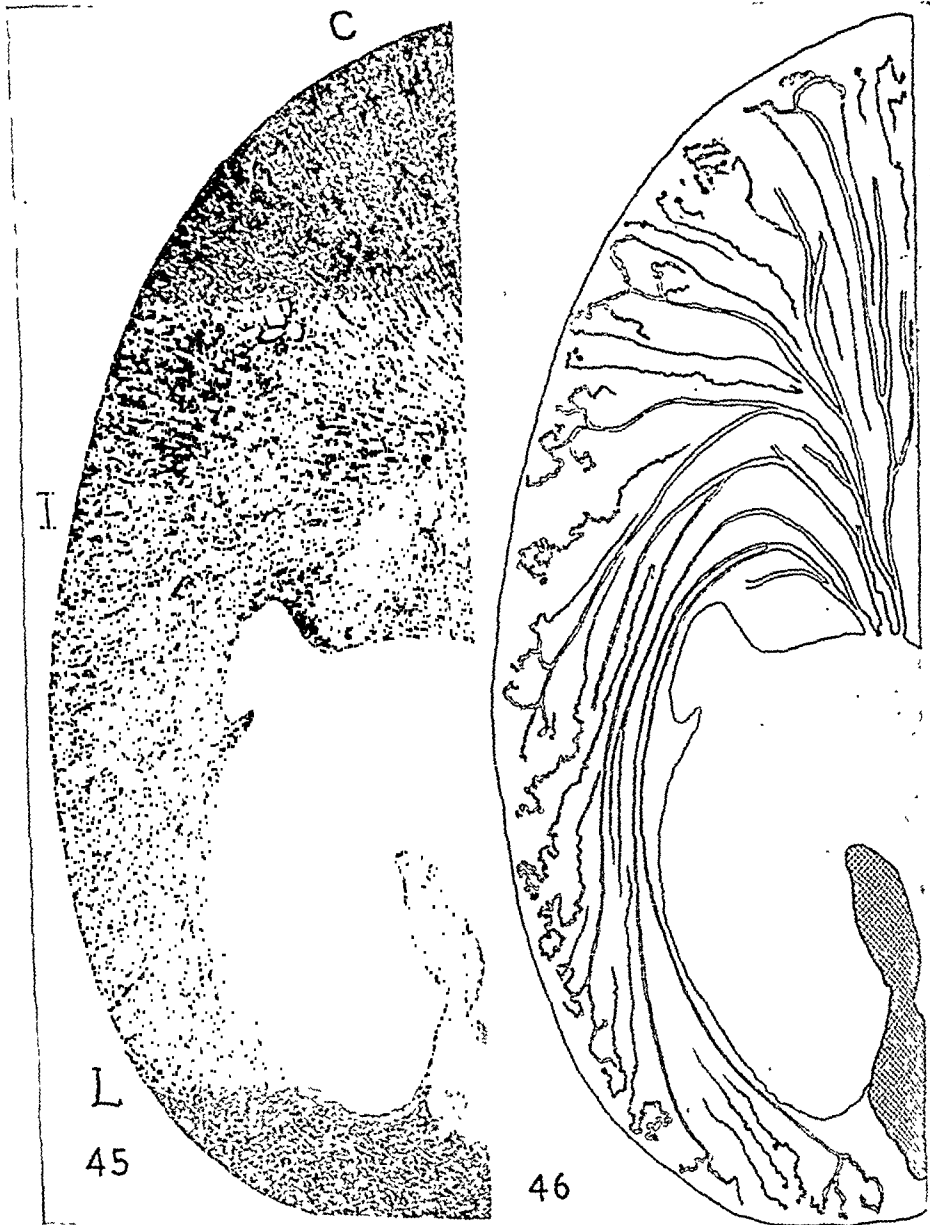


Fig. 10.—Photograph (45) of a cross hemisection of a rabbit's kidney, the ureter of which had been obstructed ten days and a diagram (46) reconstructed from tubules dissected out (after maceration in hydrochloric acid) from rabbits kidneys obstructed six, ten, and fourteen days. The intermediate portion is less atrophic than the central (C) and lateral (L) portions. (From Strong, Kenneth C.: *Arch. Path.* 29: 77, 1940).

Strong (Fig. 12)? Perhaps both these processes occur. The method of maceration and dissection is incompetent to answer this question fully (Fig. 13). With increasing difficulty and uncertainty are the delicate, thin-walled ducts teased out intact from the matrix of connective tissue embedding them deeper and deeper as hydronephrotic atrophy progresses. An isolated portion believed to be the one remnant of a unit may be an artifact of the method, a portion broken off from the whole by the dissecting needles. Even the disconnection of tubules and glomeruli which Oliver found in chronic nephritis and cited as evidence of continuing but unconnected activity may be so interpreted. "Two very old histologic methods have demonstrated that a tubule may persist in hypertrophic form when its glomerulus is reduced to an almost bloodless mass of collagen



Fig. 11.—Tubular changes. The end stages of hydronephrotic atrophy as demonstrated by maceration and needle dissection (Johnson 1932). Some Bowman's spaces with glomeruli in fairly good condition empty (glomerular filtrate) directly through dilated ducts into the distended pelvis, the content of which is now a filtrate. Tubular function has ceased. Back-flow possibly occurs up some of these ducts through glomeruli with low pressure. (From Johnson, Clark M : J. Urol. 27: 279, 1932.)

(Oliver, 1933), that the disruptive processes of disease *may cut off tubules from glomeruli*, and that these isolated tubules not only survive but maintain evidence of vital progressive changes" (Oliver, 1935). In Fig. 14 is shown Oliver's aglomerular tubule and atubular glomerulus but the chances, inherent in the method, that these "two blind ends" have been torn apart or that this glomerulus belongs to another tubule and the tubule to another glomerulus leave some doubt of Oliver's interpretation. Elsewhere he shows intact atrophic units (Fig. 15). Strong grants that tubular remnants are "undissectable" and "unidentifiable" in any portion after 114 days. Yet even after the removal of much longer obstructions, enough of them remain intact to form a repair nodule,* and glomeruli, tubular remnants, and dilated collecting ducts survive obstruc-

*Thus explaining the meaning of the term "group distribution" which Strong questions on page 116 of his paper.

tions more than twice as long. The conclusions based on this method alone, therefore, are not convincing.

Arterial Changes.—The arterial changes can be demonstrated satisfactorily by methods of celluloid corrosion (Fig. 16), x-ray stereopticon (Fig. 17), and injections of Berlin blue (Fig. 18). The corticomedullary line is drawn on both

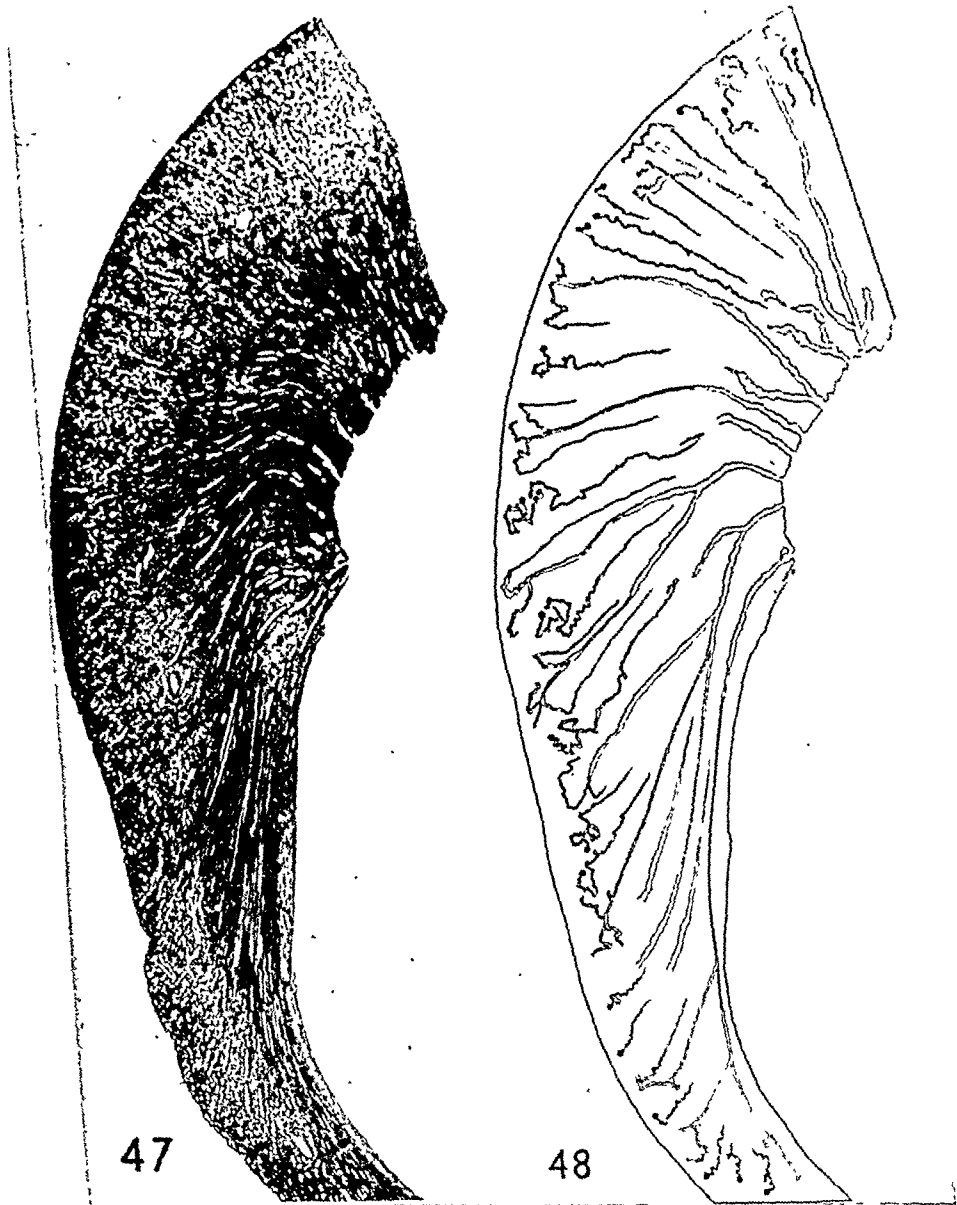


Fig. 12. Photograph (left) of one half a cross section of a rabbit's kidney obstructed twenty-eight days, and (right) of a corresponding area reconstructed from tubules dissected out from the corresponding area of kidneys obstructed twenty-one and twenty-eight days. Very few convoluted tubules were seen in the latter, many apparently had blind endings, yet a rabbit's kidney obstructed twice as long or longer will show considerable repair after removal of the obstruction. (From Strong, Kenneth C.: *Arch. Path.* 29: 77, 1940.)

vascular and tubular distinctions; above it are glomeruli and the efferent capillary plexus, below it, arteriolae rectae and the collecting tubules (Fig. 19). All tubular convolutions are above, while the medullary loops and collecting ducts lie mainly below. Some semblance of the foregoing vascular division on this line remains throughout progressive hydronephrotic atrophy, as . . . be

shown by the methods described, so that the tubular distribution above and below it must likewise persist in some form. As the interlobar and arcuate vessels stretch and their calibers diminish with pelvic distention, only those interlobular arteries which have not been shut off by the compression continue supplying blood to their glomeruli and these, through postglomerular capillary plexuses and arteriolae rectae, continue to nourish the corresponding tubular

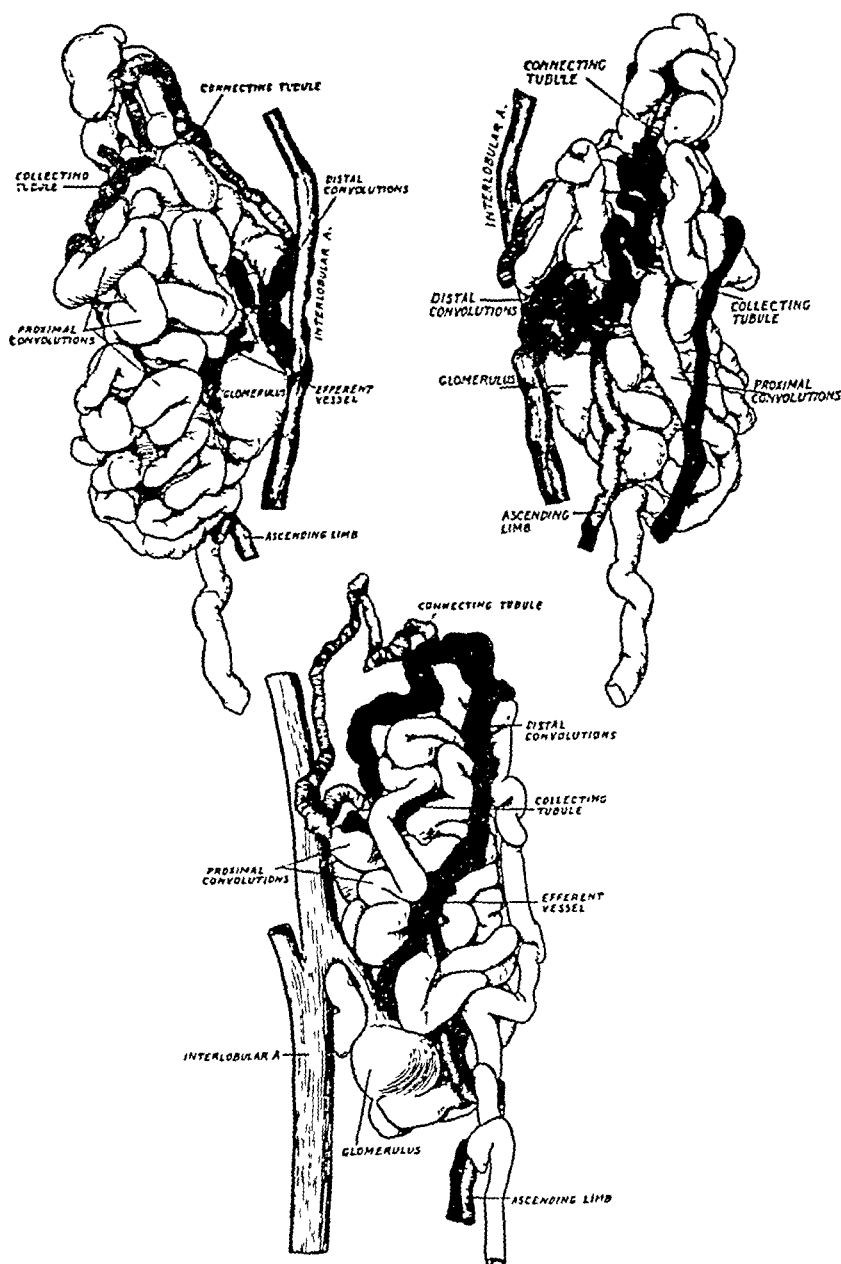


Fig. 13.—Glomerulo-tubular units isolated after maceration by needle dissection. (From Oliver, J., and Lund, E.: *Arch. Path.* 15: 755, 1933.)

components. This leads to great differences in the rate of progress of hydronephrotic atrophy throughout the parenchyma of the same kidney. Those parts disappearing first have the poorest blood supply and vice versa. This accounts for the group distribution of survival, permitting isolated repair nodules in experimental hydronephrosis. The elongation and thinning out in caliber of

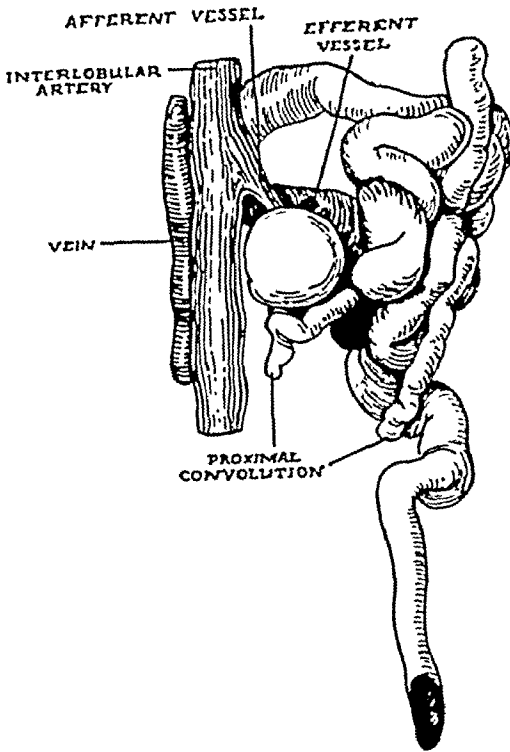


Fig. 14.—The finding which might point to independent function of glomeruli (atubular) and tubules (aglomerular). (From Oliver, J., and Luey, A.: Arch. Path. 19: 1, 1935.)

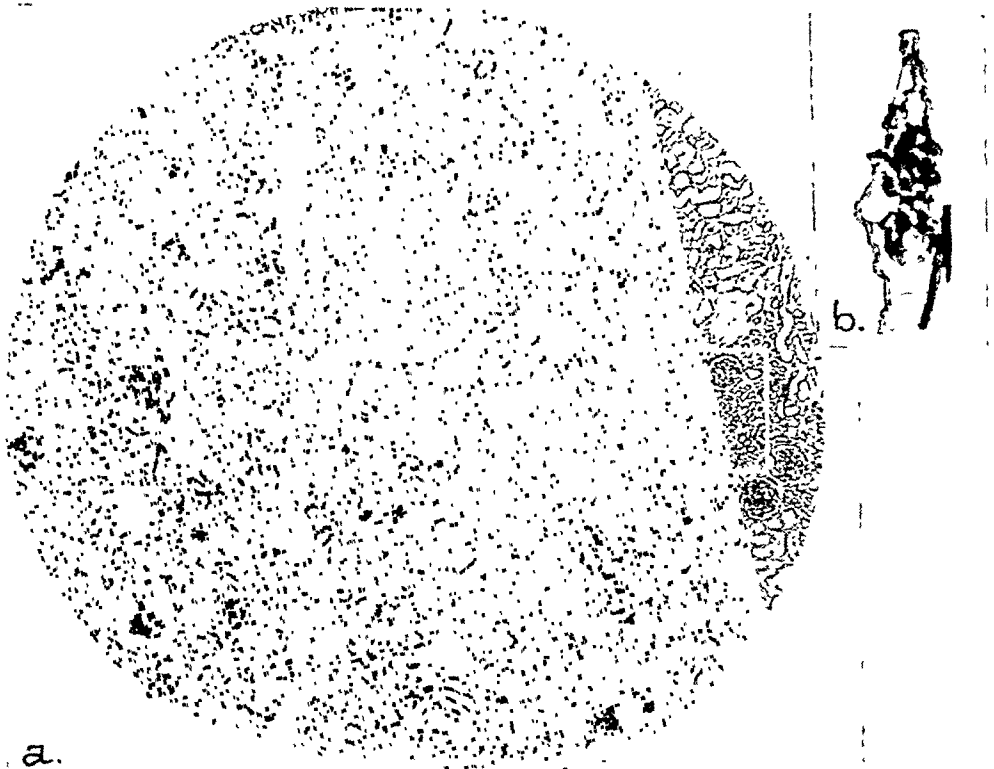


Fig. 15.—Glomerulo-tubule dissection. *a*, Photomicrograph showing a hypertrophic (right) and an atrophic (left) glomerulo-tubule in the same section. *b*, Photograph of one such atrophic glomerulo-tubule after dissection by needle dissection. (From Oliver, J., and Lund, E.: Arch. Path. 15: 755, 1933.)

the main arterial subdivisions, that is, the interlobar and arcuate branches, are accompanied by shrinkage of the interlobular arteries with attenuation of the capillary plexus of the cortex and tortuosity of arteriolar rectae of the medulla (Fig. 20). There is considerable difference later in the size of glomeruli (denied by Strong), which would indicate the possibility of compensatory hypertrophy of some glomeruli, similar to that observed by Oliver in chronic nephritis.

Venous Changes.—The venous changes are best shown by x-ray stereopticon (Fig. 21) and injections of Berlin blue (Fig. 22). The general changes are similar to those of accompanying arteries.

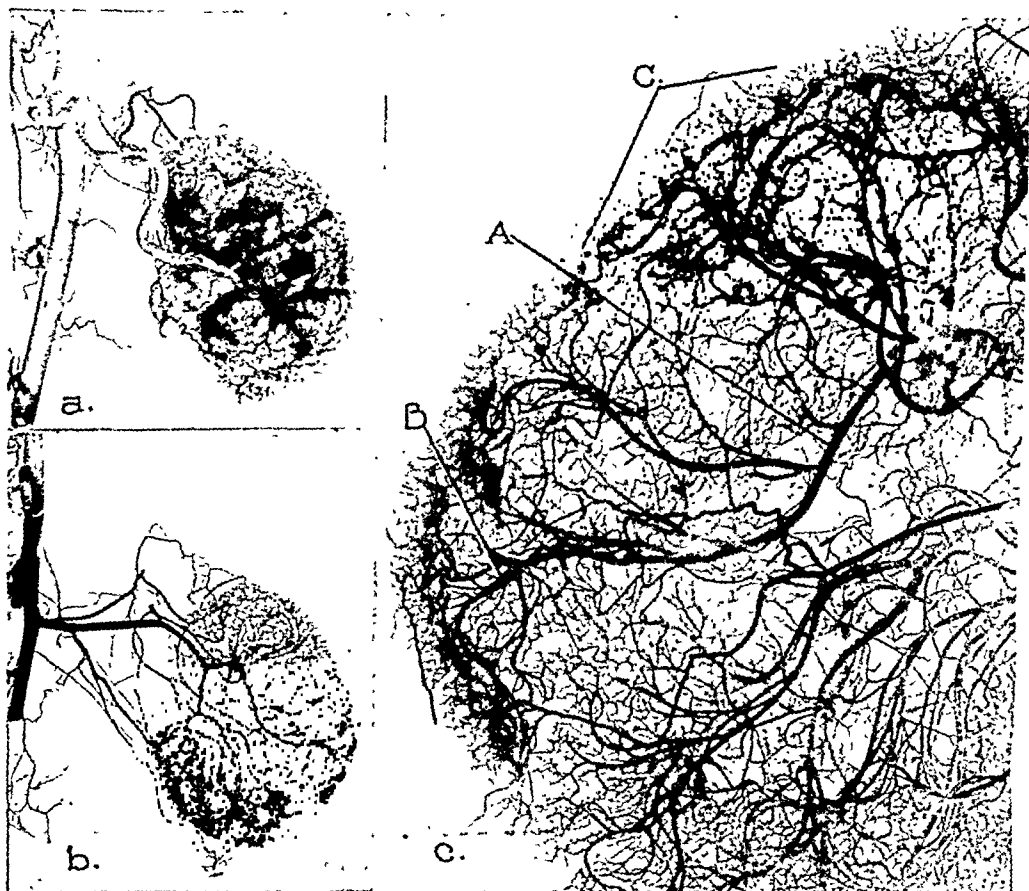


Fig. 16.—Arterial changes in the hydronephrotic kidney of the rabbit, as demonstrated by collodion injections. *a*, twenty-one days: The pelvis has also been injected and shows how the circulatory tree is compressed and stretched by the progressive pelvic enlargement. The interlobular arteries at the rim are still numerous and fairly straight. *b*, twenty-six days: Marked elongation of the interlobar arteries with foreshortening and tortuosity of the interlobular arteries. *c*, Enlargement of a portion of *b*, showing clearly the increase in length and the diminution in caliber of the interlobar (*A*) and the arcuate arteries (*B*), and the marked change in the interlobular arteries (*C*). (From Hinman, F., and Morison, D. M.: *J. Urol.* 11: 131, 1924.)

DISCUSSION

When the tubular and vascular alterations mentioned are related one with the other, it is seen that two pathologic processes produce hydronephrotic atrophy. Undoubtedly, tubular and pelvic distention cause pressure atrophy, but the effect of this distention on blood supply superimposes an anemic atrophy. Levy, Mason, Harrison, and Blalock have shown the great reduction in the flow of renal blood in simple hydronephrosis, and if this reduction is increased by arterial constrictions or ligations, atrophy and dilatation are accelerated (Fig. 23). The sudden increase of pelvic contents at from fourteen to twenty-eight days of obstruction (Table II) is not readily explainable. It may possibly be

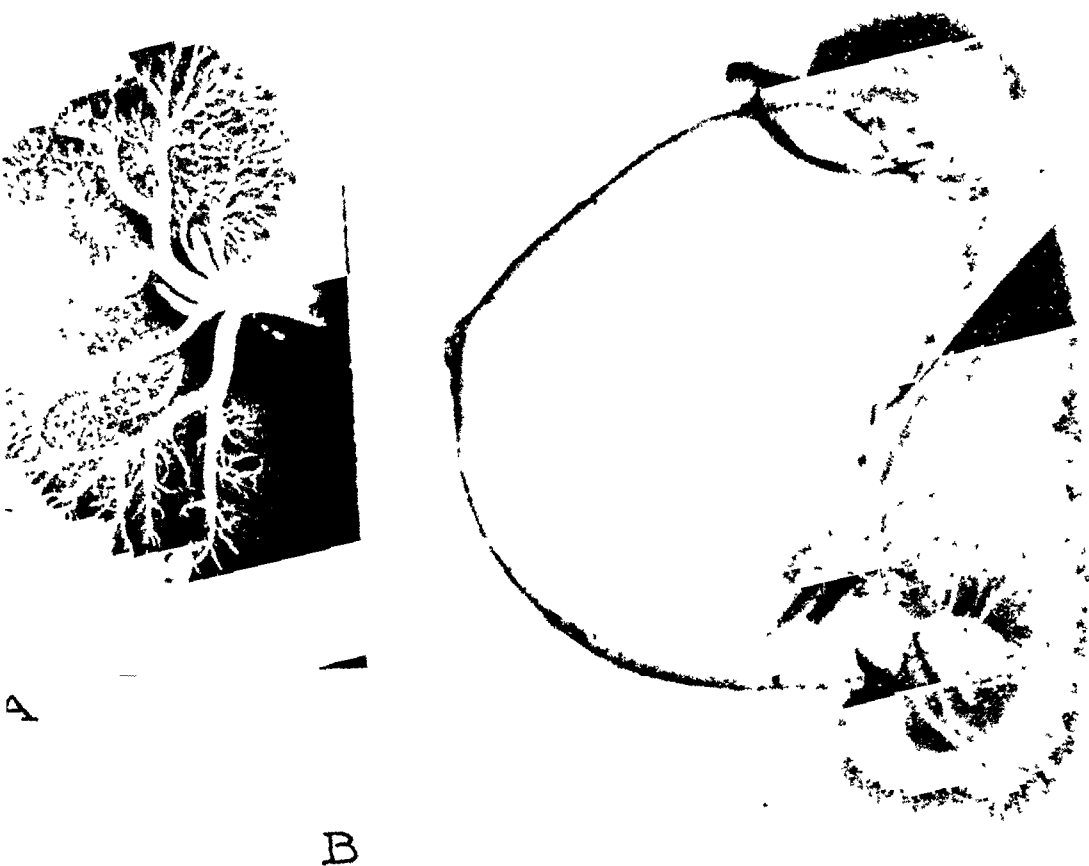


Fig. 17.—Arterial changes. A, Normal, note the size at the base, and the direct branching to small straight interlobular arteries. B, Hydronephrosis (pyelectasis demonstrated by distention with air). Note the group distribution of arteries (vessel to lower pole not injected) and their long, arched, tapering course to the foreshortened, crooked interlobular arteries. (From Hinman, F., and Morison, D. M.: *J. Urol.* 11: 131, 1924.)



Fig. 18.—Photograph of a late stage of hydronephrotic atrophy (rabbit) after injection with Berlin blue, showing the few groups of resistant glomeruli about the interlobular arteries least constricted. (From Hinman, F.: *Surg. Gynec. & Obst.* 58: 356, 1934.)



Fig. 19.



Fig. 20.

Fig. 19.—Arteriolae rectae (Berlin blue) below the corticomedullary line of a normal kidney. (From Hinman, F., Morison, D. M., and Lee-Brown, R. K., *J. A. M. A.* 81: 177, 1923.)

Fig. 20.—Arteriolae rectae (Berlin blue) in a hydronephrotic kidney (rabbit). (From Hinman, F., and Morison, D. M.: *J. Urol.* 11: 131, 1924.)

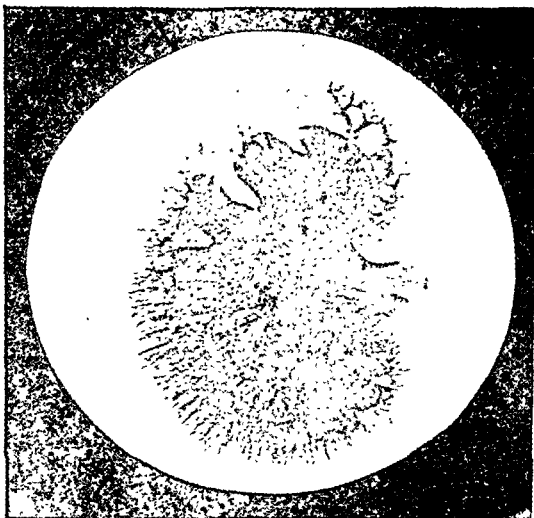


Fig. 21.

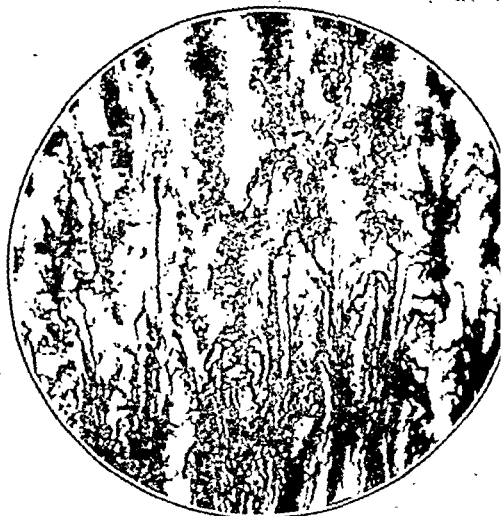


Fig. 22.

Fig. 21.—Venous system of the kidney of a sheep which has been injected by way of the ureter, showing the radial course of the interlobular vessels and the circumferential direction of the larger arcuate branches. The pelvis is well outlined and the rupture has occurred in a minor calix. (From Hinman, F.: *Surg. Gynec. & Obst.* 58: 356, 1934.)

Fig. 22.—Photograph at the corticomedullary line after venous injection (Berlin blue), showing the secondary capillaries in the form of plexuses about convoluted tubules of the cortex, and the venae rectae, in the form of cylinders about Henle's loops of the medulla. (From Hinman, F., Morison, D. M., and Lee-Brown, R. K.: *J. A. M. A.* 91: 177, 1923.)

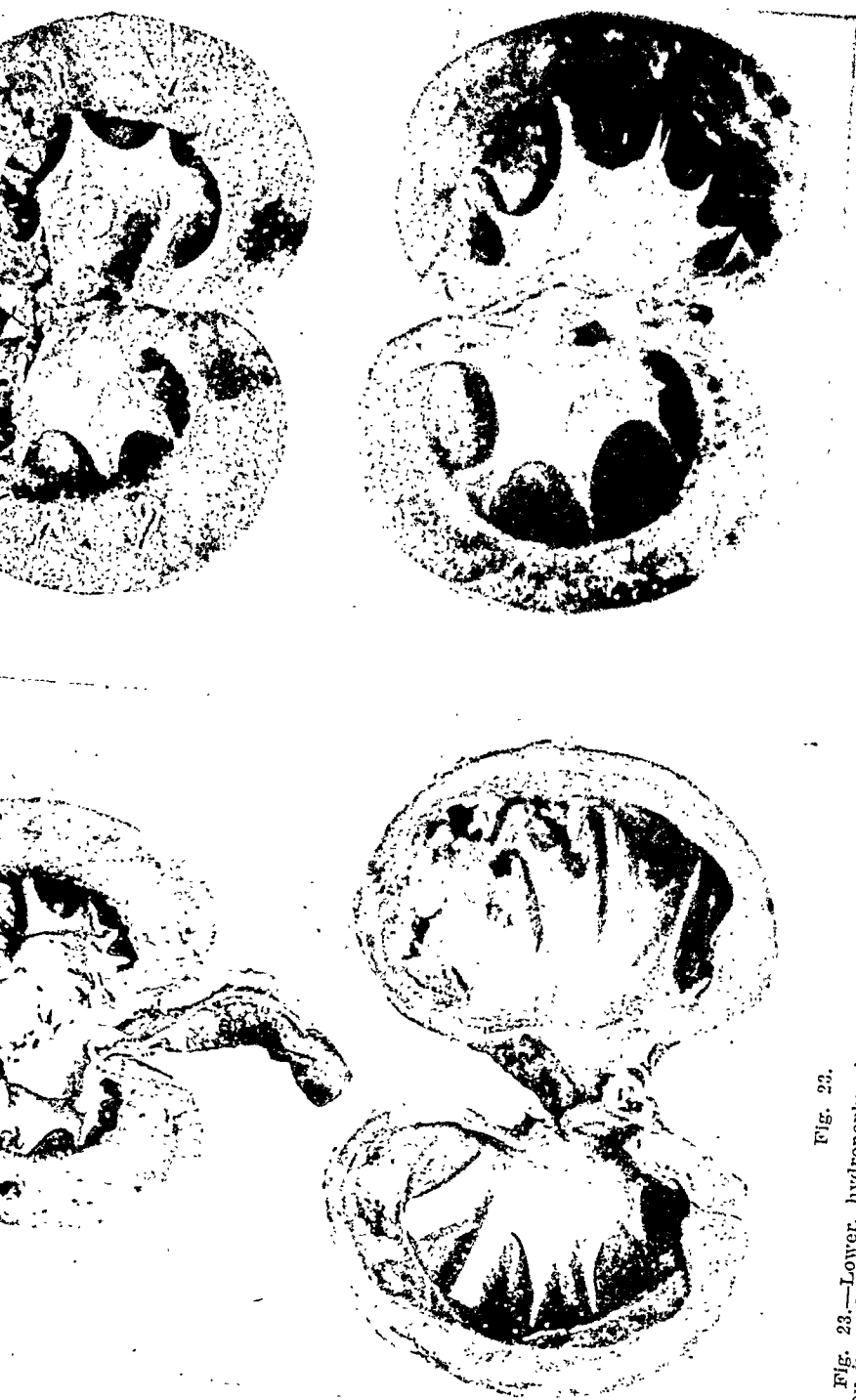


Fig. 23.

Fig. 23.—Lower, hydronephrosis of fourteen days' duration in a dog with partial compression of the renal artery; the upper kidney is used for comparison, and represents the degree of hydronephrosis seen with simple ureteral obstruction for the same period. Note the remarkable acceleration in the rate of hydronephrotic atrophy when the artery is compressed. (From Hinman, *Principles and Practice of Urology*, Philadelphia, 1933, W. B. Saunders Company.)

Fig. 24.

Fig. 24.—Lower, hydronephrosis following twenty-one days of complete obstruction together with partial compression of the renal vein, showing a greater degree of dilatation than that which occurred with simple hydronephrosis (upper) lasting the same period. (From Hinman, *Principles and Practice of Urology*, Philadelphia, 1933, W. B. Saunders Company.)



Fig. 19.



Fig. 20.

Fig. 19.—Arteriole rectae (Berlin blue) below the corticomedullary line of a normal kidney. (From Hinman, F., Morison, D. M., and Lee-Brown, R. K., *J. A. M. A.* 81: 177, 1923.)

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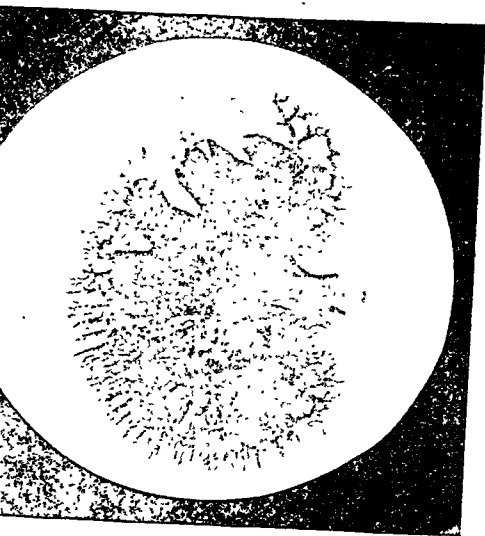


Fig. 21.

Fig. 21.—Venous system of the kidney of a sheep which has been injected by way of the ureter, showing the radial course of the interlobular vessels and the circumferential direction of the larger arcuate branches. The pelvis is well outlined and the rupture has occurred in a minor calix. (From Hinman, F.: *Surg. Gynec. & Obst.* 58: 356, 1934.)

Fig. 22.—Photograph at the corticomedullary line after venous injection (Berlin blue), showing the secondary capillaries in the form of plexuses about convoluted tubules of the cortex, and the venae rectae, in the form of cylinders about Henle's loops of the medulla. (From Hinman, F., Morison, D. M., and Lee-Brown, R. K.: *J. A. M. A.* 91: 177, 1923.)



Fig. 22.

CONCLUSION

Even after many years of study by many different men, the structural changes of hydronephrosis are poorly understood.

REFERENCES

- Bowman, William: On the Structure and Use of the Malpighian Bodies of the Kidney, With Observations on the Circulation Through That Gland, London, 1812, R. and J. E. Taylor, pp. 57-80.
- Cohnheim, J.: Vorlesungen über allgemeine Pathologie, Berlin, A. Hirschwald, 1880.
- Fabian, E.: Pathologie und pathologische Anatomie, in: Bern, G., and Flügge, K.: Bibliotheca medica, vol. 18, Cassel, 1904, T. G. Fischer & Co., p. 1.
- Fuchs, F.: The Flow of Water Through the Kidney, New York, 1911, Manhattan Printing Co.
- Henle, F. G. J.: Allgemeine Anatomie, Leipzig, 1811; Beiträge zur Anatomie und Embryologie, Bonn, 1882.
- Hinman, Frank: The Principles and Practice of Urology, Philadelphia, 1935, W. B. Saunders Company.
- Hinman, Frank, and Hepler, A. B.: Experimental Hydronephrosis. The Effect of Ligation of One Branch of the Renal Artery on Its Rate of Development, IV. Simultaneous Ligation of the Posterior Branch of the Renal Artery and the Ureter on the Same Side, Arch. Surg. 12: 830-853, 1926.
- Huber, G. Carl: The Morphology and Structure of the Mammalian Renal Tubule, The Harvey Lectures, Lancaster, Pa., 1909-10, Science Press Printing Company, pp. 100-149.
- Johnson, C. M.: The Pathogenesis of Hydronephrosis, J. Urol. 27: 279-293, 1932.
- Levy, S. E., and others: The Effects of Ureteral Occlusion on the Blood Flow and Oxygen Consumption of the Kidneys of Unanesthetized Dogs, SURGERY 1: 238-242, 1937.
- Malpighi, M.: Discours anatomiques sur la structure des viscères, scavoir du foye, du cerveau, des reins, de la ratte, du polype du doeur et des poumons, Paris, 1687, L. d'Houry, pp. 374.
- Oliver, J., and Lund, E. M.: Plastic Studies in Abnormal Renal Architecture; I. The Two Architectural Units in Chronic Bright's Disease and Their Possible Functional Significance, Arch. Path. 15: 755-774, 1933.
- Oliver, J., and Luey, A. S.: Plastic Studies in Abnormal Renal Architecture; II. The Morphology of the Abnormal Nephron in Terminal Hemorrhagic Bright's Disease, Arch. Path. 18: 777-816, 1934, III. The Agglomerular Nephrons of Terminal Hemorrhagic Bright's Disease, Ibid. 19: 1-23, 1935.
- Oliver, J.: Architecture of the Kidney in Chronic Bright's Disease, New York, 1939, Paul B. Hoeber, Inc.
- Peter, K.: Untersuchungen über Bau und Entwicklung der Niere, Jena 1909, Gustav Fischer.
- Ponfick, E.: Ueber Hydronephrose, Beitr. z. path. Anat. u. z. allg. Path. 49: 127-212, 1910.
- Schweigger-Seidel, F.: Die Nieren des Menschen und der Säugethiere in ihrem feineren Baue geschildert, Halle, 1865, pp. 88.
- Strong, K. C.: Plastic Studies in Abnormal Renal Architecture; V. The Parenchymal Alterations in Experimental Hydronephrosis, Arch. Path. 29: 77-119, 1940.
- Suzuki, E. T.: Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen, Jena, 1912, Gustav Fischer.
- Traut, H. F.: The Structural Unit of the Human Kidney, Contributions to Embryology No. 76, Pub. 332, Washington, D. C., 1923, Carnegie Institution of Washington, pp. 103-120.

HYDRONEPHROSIS

II. THE FUNCTIONAL CHANGES

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INTRODUCTION

ALMOST two decades should have increased our knowledge of hydronephrosis. The advances, however, have been largely in the surgical field; little has been added to the fundamentals of pathology and diagnosis. Nevertheless, this offers a somewhat better understanding of what has long been a pathologic enigma. Primary atrophy and quick death are the doom of other glands after complete obstruction of their ducts. The kidney meets its inevitable end differently. The destruction is prolonged for months and, should obstruction be relieved before the complete ruin of all its secretory units, these few will recover and still function. Hydronephrotic atrophy is distinct and separate from primary or any other kind of atrophy. It is unique, and its mechanism is almost as dimly glimpsed as is that of the secretion of the urine. The surgical advances have been mostly in the relief of obstructions at the ureteropelvic juncture and the methods, rarely original but borrowed largely from those used in relieving similar intestinal obstructions, are new to urology and mark an advance in this specialty. Nevertheless, like all things in medicine when new, they are overdone. Conservation by plastic surgery has about reached its zenith of popularity and from now on the renal surgeon, having gone through the stage of convincing himself or being convinced that he can repair everything, perhaps occasionally will ask himself before operating, what good will operation do this patient? The conservative surgeon of the future will not be the one now so considered, who removes only the functionless kidney, repairing all the others. After all, this policy of surgical repair so boastfully endorsed by many shows operative skill only without understanding or judgment of renal physiology. These two aspects, therefore, namely *pathogenesis* and *surgical treatment*, will be particularly discussed and modernized in this and the papers to follow.

Definition.—Hydronephrosis is the term applied to the renal changes of distention and atrophy which follow urinary obstruction. The fluid causing the distention is urine, and the condition presupposes continued secretion of urine in spite of the obstruction. The content of the sac becomes more dilute as the degree of hydronephrosis progresses, until, in the final stages of complete hydronephrotic atrophy, it is nothing but water and salt. The term hydronephrosis appeared first in Rayer's *Traité des Maladies des Reins* (1841). Hydrops renales (Rokitansky), hydrops renis (Martineau), uronephrosis (Guyon and Albarran), sacknière (Küster), nephrohydrosis (Aschoff), and nephrectasis (Morris) have been used as synonyms. The condition is, of course, to be distinguished from cystic changes in the kidneys such as solitary cyst and polycystic kidneys. Furthermore, the condition is not to be confused with pyonephrosis which was the term applied by Roberts, in 1896, to a suppurating hydronephrosis, but has since

come to define a completely obstructed kidney full of pus that follows progressively a pronounced pyelonephritis. A suppurating hydronephrosis is differentiated by the term infected hydronephrosis, but with severe pyelonephritis an infected hydronephrosis may undergo secondary atrophy and become a pyonephrosis. In the following pages, the term *hydronephrosis* will be applied to renal changes of obstruction without infection; that of *infected hydronephrosis*, to the foregoing condition which has a secondary infection imposed on it; and *pyonephrosis* is used to describe a kidney full of pus, without function, and with little if any pelvic distention. Whatever distention may be present is caused by pus rather than urine.

The modern hypothesis put forward to explain renal activity of filtration reabsorption with some secretion is not too secure. One weakness is that our growing understanding of what goes on in hydronephrosis tends to undermine the theory as it now stands. Perhaps one or another of the types of backflow in hydronephrosis is not solely pathologic. Of this we are uncertain, but likewise we are still uncertain about many of the structural changes (Hinman) occurring in hydronephrosis and without knowing these, correlation between structure and function is as impossible as reconciliation of normal and hydro-nephrotic functions. That, with one exception, renal activity of some kind continues after complete ureteral obstruction is certain. This exception is anuria with which hydronephrosis never develops. Every hydronephrotic kidney is a functioning kidney. This was the idea in mind in comparing the contents of the kidney to a fresh-water lake, an inflow and an outflow. Strong (see page 110 of reference) objects to this simile: "Although the pelvic content obviously is not 'stagnant' it at no time resembles a 'fresh-water lake.' It is commonly acknowledged that the pelvic fluid quickly loses the character of urine, and it must therefore be granted that the organ has ceased to function as a kidney." This statement cannot be granted since, with partial obstructions, the kidney functions and, except for the rate of production, the pathologic changes are indistinguishable from those present with complete obstruction. Too little attention has been paid to these functional changes which may have considerably more significance in renal physiology than anyone suspects.

FUNCTIONAL CHANGES

That the content of the renal pelvis is not simply an accumulation can be shown in several ways. If 1 c.c. of phenolsulfonphthalein is put in when the ureter is tied, the dye will disappear within forty-eight hours (Table I). An-

TABLE I. DISAPPEARANCE OF PHENOSULFONPHTHALEIN FROM AN OBSTRUCTED PELVIS OF THE RABBIT'S KIDNEY

	LEFT URETER INJECTED WITH FROM 1 TO 1.5 C.C. OF DYE, DOUBLY LIGATED AND DIVIDED, IN RABBITS	AMOUNT OF URINE IN PELVIS (C.C.)	PER CENT OF PHTHALEIN
After 24 hours	1	2.5	40
	2	3.0	12
	3	3.0	Trace
After 48 hours	4	3.0	0
	5	3.0	8
	6	2.5	Very faint trace
After 96 hours	7	4.0	0
	8	4.0	Trace
After 168 hours	9	Not estimated	0
	10	6.0	0
	11	6.0	0

(From Hinman, F., and Veckl, M.: J. Urol. 15: 267, 1926)

analyses of the content also show that, except for red blood cells and albumin from trauma in earlier stages, it resembles more and more that of the glomerular filtrate. Intrapelvic pressures also gradually diminish as hydronephrosis progresses, as do recoveries of function after removal of the obstruction. These and other facts indicate that renal work of some kind goes on for some time after the ureter is tied. Since the products of excretion cannot drain off by the usual route, some other pathway must be used. A probable one is tubular reabsorption in excess of normal. Through the tubules are sucked back huge amounts of water, about 90 per cent of the glomerular filtrate (Richards) and probably as much as 99 per cent in oliguria. The structural plan of loops in a capillary net is perfect for reabsorption. Nevertheless, that route, effective through osmosis only, is thought by many to be insufficient to explain the mechanism in hydronephrosis. Moreover, Henle loops soon disappear.



Fig. 1.—Drawing of a minor calyx; the fornix calicis is at 2. (From Narath, P. A.: *J. Urol.* 43: 145, 1940.)

The capillaries of a glomerulus are directly in contact with the lining of Bowman's capsule. There is no interstitium. Throughout the kidney elsewhere, with one exception, tissue spaces separate tubules and vessels and these spaces often show the accumulation of fluid present in edema. The one exception is the fornix calicis (Fig. 1). At this point the calical or, in unipapillary kidneys, the pelvic epithelium joins that covering the papilla at an acute angle and in this transition acquires endothelial properties by which a direct relationship to capillaries, very similar to that in glomeruli, is established. It is possible that under certain conditions of diuresis (Fuchs, 1936, 1937, 1938) or of peristalsis

(Narath, 1940), absorption of total urine may occur physiologically without fornical rupture.

Overtaxation of the transportation system in extreme polyuria is prevented by means of the fornical apparatus. The progressive loss of muscular tonus of pyelon and calices during an increase in diuretic rate induces progressive extension of the fornical mucosa and fornical reabsorption sets in. Thus, such an amount of total urine as is excreted by the kidney in excess of the transportation capacity of the pyelon and ureter is reabsorbed by the fornical apparatus, and any increase in intrapelvic pressure that might interfere with continual renal excretion is prevented. The processes going on within the kidney have acquired independence of the facilities for urinary transportation toward the bladder. . . . Thus, renal excretion is independent of urinary retention. Prolonged retention in coincidence with polyuria, as well as extreme polyuria alone, can create a discrepancy between diuresis (as subordinated to metabolic exigencies) and transportation facilities

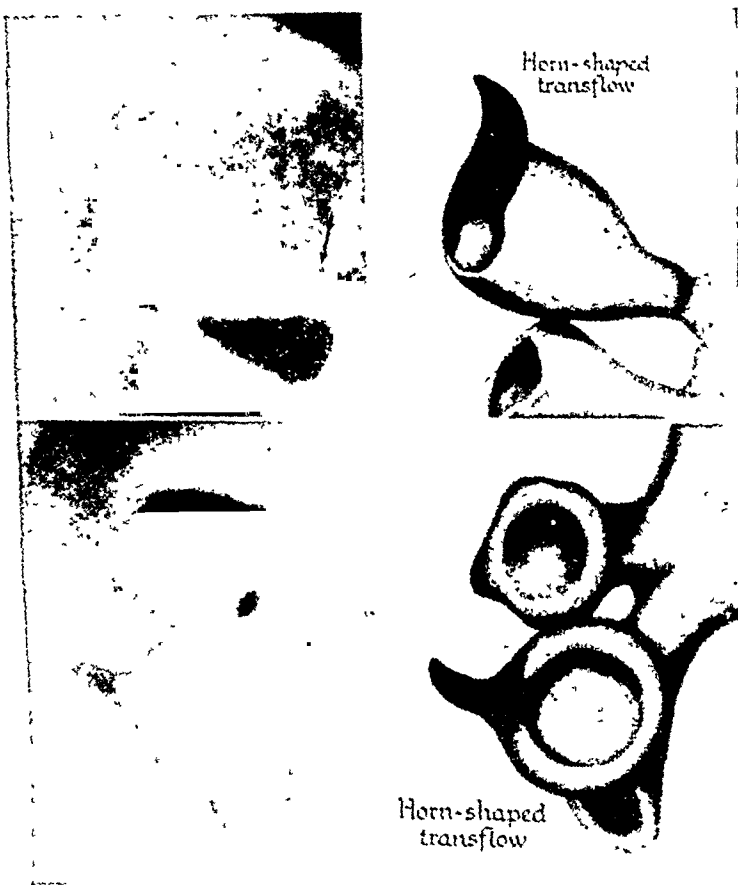


Fig. 2.—Narath's idea of physiologic transflow. (From Narath, P. A.: J. Urol. 43: 145, 1940.)

(as partly subordinated to the relations with the environment). That discrepancy is solved first by means of the tonus. After having reached the limits of tonus regulation, fornical reabsorption eventually sets in thus rendering the kidney rather free to do its excretive work. Thus homeostasis of intrarenal conditions is partly achieved by interpolation of the fornical apparatus between the kidney and the outside world. (Fuchs, 1944.)

It is possible to rupture the fornix with syringe pressure as well as gravity methods in the course of retrograde pyelography and to press the contrast medium into the sinus renalis and even further up, injuring the venous system as we shall see later. I want to emphasize, however, that in our investigation the rise in pressure is produced by the kidney and the renal pelvis alone. If we still believe that we deal with a rupture of the fornix, then we must believe, too, that every

colic, even a slight one, ruptures the fornix of the calyx. I saw these absorptive processes starting, however, at a moment when the pressure was not felt at all by the patient or the increase in pressure caused only a slight discomfort. Furthermore, there are observations reported in the literature which find their explanation only by an absorptive process. (Narath, 1910.) (Fig. 2.)

Since pyelovenous backflow is possible physiologically (Fuchs and Narath), it would be much greater after ureteral obstruction. Winton (1937), after studying the relationship of blood pressure to ureteral pressure, put it as follows:

It is clear that the experimental evidence, underlying the pressure-flow relations which are implicit in the filtration-reabsorption theory, is far from satisfactory, and as long as this remains so, renal physiology can hardly be regarded as secure from an intrusion by the unexpected (p. 432). . . . The simplest escape from these difficulties, compatible with the filtration-reabsorption hypothesis in its original, or in its modern form including secretion of some substances into the tubules, is to suppose that when flow from the ureter ceases, urine flow down the tubules still takes place, this urine leaking back into the blood at some point distal to the site of reabsorption of water (p. 429).

The main controversy now hinges on the site or sites of this backflow or reabsorption. It may be refreshing to the reader to quote someone else's exposition of it. (The Pathogenesis of Hydronephrosis, Surg., Gynec. & Obst. 58: 356-376, 1934.)

In complete ureteral obstruction and to a minor degree in partial obstruction, multiple fornical ruptures occur and through them free flow of urine and transmission of pressure from the pyelon to the fluid within the sinus are established. When the pyelon is markedly distended, intra-abdominal pressure is transmitted through the peritoneum upon the pelvic contents and thence on the edema. Pressures of 300 mm. Hg may thus reach the tissue spaces of the kidney, though only intermittently and for short periods. The continuous intrapelvic pressure is about 30 mm. Hg in oliguria and about 70 mm. Hg in polyuria. Since soon after the onset of the transfornical edema polyuria becomes constant, only the latter value should be considered. The edema within the sinus compresses the veins, and cyanosis of the kidney results. As soon as pyelovenous backflow is established into the interlobar veins within Bertin's columns, many flows are established between the ruptured fornices and the veins. Along these flows there are pressure slopes from 70 mm. Hg down to near 0. Thus, the venous compression is partly relieved and venous blood flow resumed, the cyanosis disappearing. While pyelovenous backflow involves many interlobar veins, it never involves all of them. Some interlobar veins are simply compressed by the edema which proceeds along the veins toward the corticomedullary boundary and thence along the interlobular veins toward the cortex and the subcapsular space. When this occurs, abundant lymphatic reabsorption sets in, the lymphatics being highly dilated. There is a pressure slope between the fornices and the subcapsular space, as the main place of lymphatic reabsorption. The pressure of the edema is lowest near the surface of the kidney while it is still rather high at the corticomedullary boundary. The relatively high pressure at the corticomedullary boundary is transmitted upon the tissue fluid within the pyramids along the convex vertical column. Thus the pressure of the transfornical edema is highest within the medulla (the pyramids). The pressure is lower within the cortex owing to subcapsular lymphatic reabsorption, and it is also lower within most of Bertin's columns owing to pyelovenous backflow occurring within them. . . . In the third week of obstruction, with complete disappearance of the fornices, of course fornical rupture and pyelovenous backflow are a thing of the past. The transfornical edema disappears. The interstitial spaces are progressively filled by newly formed connective tissue. Damage to Malpighi's corpuscles, while still comparatively slight, is irregular, some glomeruli working with a higher filtration pressure than others. Therefore,

glomerular filtrate produced in some part of the parenchyma reaches the pylon and proceeds thence into collecting tubules of a different part of the parenchyma and finally reaches glomeruli with decreased or completely eliminated filtration pressure. A sufficient difference in blood pressure in two major groups of glomeruli causes back filtration into the low pressure glomeruli of the filtrate of the high pressure glomeruli. Thus, the flow of urine never ceases, pyelovenous backflow and lymphatic reabsorption having been substituted by glomerular back filtration. The circulating urine is rather identical with glomerular filtrate owing to the



Fig. 3—Pyelovenous backflow demonstrated by collodion (A and B) and Berlin blue (1 and B, from Hinman, F., and Lee-Brown, R. J. A. M. A. 82: 607, 1924). (C) Injections of the renal pelvis by way of the ureter (rabbit) (From Hinman, F., Morison, D., and Lee-Brown, R. J. A. M. A. 81: 177, 1923.)

wholesale tubular damage. The intermittent superimposition of intra-abdominal pressure brings about capillary collapse and destruction of most glomeruli after six to eight weeks of obstruction. However, some production, some flow, and some reabsorption of filtrate is going on even within the oldest hydronephrotic sacs. Morphologically the remains of the totally excavated pyramids are permanently separated from each other by the remains of atrophied Bertin's columns and the adjacent compressed interlobar vessels. (Fuchs, 1944.)

The routes of backflow of pelvic urine mentioned can be demonstrated by retrograde injections of the renal pelvis. Complete filling of the venous system is possible by way of the ureter. The rupture can be shown to have recurred in the fornix calicis (Fig. 3). Collecting ducts can be filled for a short distance only (Fig. 4), which would nullify the route via Henle loops even in the early stages before their destruction. The pressure required to cause rupture is lower than secretory pressure and once the route is opened, much lower pressures permit a backflow (Table II). This is also shown by the drop of intrapelvic pressures when backflow starts within from thirty to sixty minutes as registered on a manometer occluding the ureter. It is possible, of course, that a backflow occurs from the dilated collecting ducts into the interstitium and then into veins or lymphatics, a route favored by Narath, but as yet not demonstrated by anyone. It is by this tubular route, however, that some backflow probably occurs after papillary ligation by which the pyelovenous route is closed (Fig. 5).

TABLE II. URETERAL BACK PRESSURE REQUIRED TO PRODUCE PYELOVENOUS BACKFLOW

ANIMAL	WEIGHT	DURATION OF COMPLETE HYDRO-NEPHROSIS	STATIC PRESSURE OF PELVIC CONTENTS	INTRAPELVIC PRESSURE OF PYELOVENOUS BACKFLOW	APPEARANCE TIME OF PHE-NOLSULFON-PHTHALEIN IN URINE OF OPPOSITE KIDNEY
Rabbit	4,500 Gm.	30 days	15 mm. Hg	10 mm. Hg	20 minutes
Dog	28 lb.	70 days	21 mm. Hg	15 mm. Hg	12 minutes

(From Hinman, F., and Lee-Brown, R. K.: J. A. M. A. 82: 607, 1924.)

Drainage of urine permitting continuation of excretion explains the mechanism of hydronephrotic atrophy. This drainage may occur by the routes indicated in Table III.

Some insight into the mechanics of hydronephrosis is obtained by studying blood flow and secretory pressure. Ureteral ligation lowers both. "There was a reduction in renal blood flow in each of the eight (hydronephrosis) experi-

TABLE III. PROVED AND SUGGESTED PATHWAYS OF URINARY BACKFLOW FROM THE RENAL PELVIS

BACKFLOW AND REABSORPTION	PHYSIOLOGIC	PATHOLOGIC
By way of the collecting tubules	Through retrograde distention with transudation into pericanalicular spaces (edema) and absorption by capillaries or lymphatics (Narath)	(1) Through rupture of distended wall of tubule with extravasation into capillaries or lymphatics (2) Through slits and excavations of the torn papilla into tissue spaces around collecting tubules
By way of the calical fornices	Through interstices of transitional epithelium (endothelial-like) directly into veins or first into tissue spaces and then after hard or long extravasation into capillaries or lymphatics (occurs in polyuria [Fuchs] and under circumstances simulating antiperistalsis [Narath], in both instances without ureteral obstruction)	Through ruptures directly into veins or first into tissue spaces with extravasation into veins or lymphatics
By way of the Bowman spaces		Extravasation through Bowman cavities whose glomeruli have low pressures

ments. The percentage reduction in flow varied from 23 to 66 per cent in the different experiments, the average being 41 per cent." (Levy and others, 1937.) Ligation of a branch or partial obstruction of the renal artery has a similar effect. Ligation of the ureter and constriction of the renal artery speed up the process of hydronephrotic atrophy in spite of the diminution of blood flow and secretory pressure. If both were increased, what would the effect be? Pro-

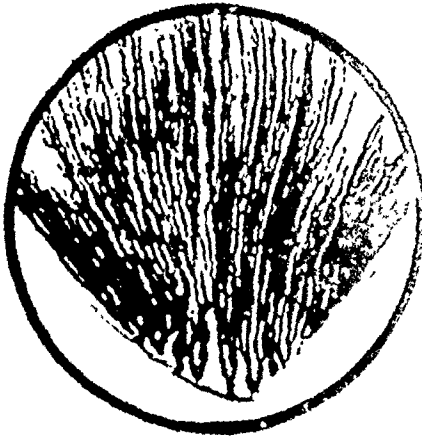


Fig. 4.—Photomicrograph of the collecting tubules at the apex of a pyramid in a sheep's kidney showing the maximum amount of tubular injection it is possible to obtain without rupture of the pelvis. (From Hinman, F., and Lee-Brown, R.: *J. A. M. A.* 82: 607, 1924.)

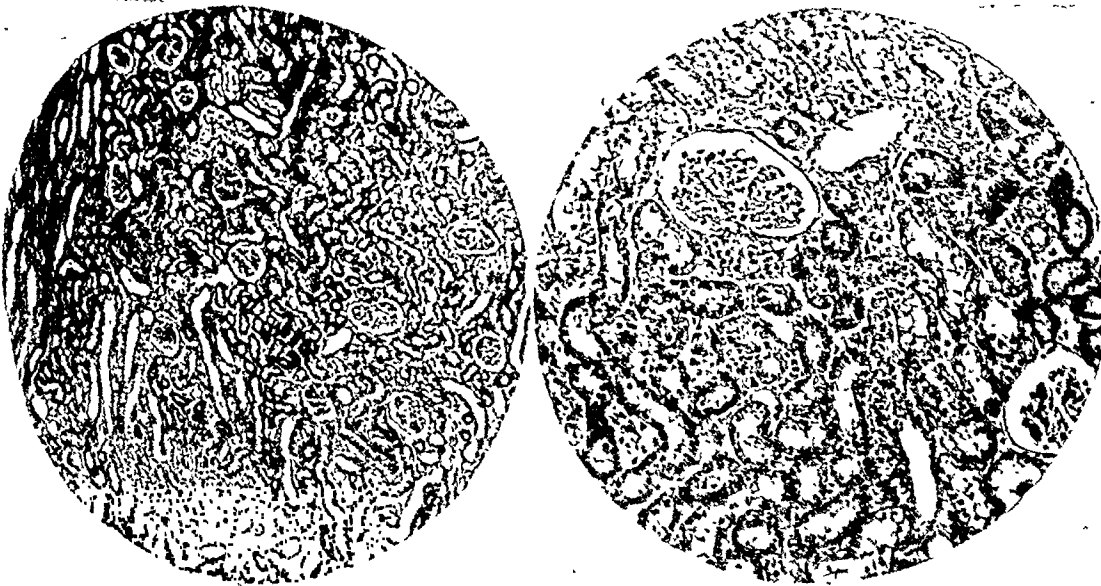


Fig. 5.—Low- and high-power photomicrographs showing the microscopic changes two weeks after papillary obstruction. The degree of dilatation is greater and the stage of hydronephrotic atrophy is more advanced (rabbit). (With Carroll.) (From Hinman, F.: *Surg., Gynec. & Obst.* 58: 356, 1934.)

longed polyuria dependent on greater blood flow and faster secretion might hasten hydronephrotic atrophy and prolonged oliguria might slow it down. Surprisingly, however, neither condition has any effect on the rate of progress. That in polyuria the function of the compensatory kidney is not in any way related can be shown by unilateral splanchnotomy (Table IV). Increasing the activity of a kidney with a tied off ureter has no effect on the standard rate of

TABLE IV

DURATION (DAYS)	WEIGHT OF RABBITS (KG.)	MEASUREMENTS OF KIDNEY (IN CENTIMETERS)			PELVIC CAPACITY (C.C.)
		LENGTH	DEPTH	WIDTH	
<i>A. Measurements of Hydronephrotic Kidney in Rabbits After Total Ligation of Left Ureter (Control Series)</i>					
7	4	5.2 (1)*	3.5 (0)	3.3 (3)	4
14	2.72	4.3 (0.55)	3 (0.48)	2.8 (0.74)	6
21	4	6 (0.9)	4.4 (0.4)	3.8 (0.76)	14
28	3.02	5 (1.13)	3.4 (0.38)	3.5 (1.21)	13
56	3	5.2 (1.36)	3.7 (0.7)	3.5 (1.22)	25
90	2.89	5.5 (1.8)	3.8 (0.91)	3.6 (1.41)	33
<i>B. Measurements of Hydronephrotic Kidney After Total Ligation of Left Ureter and Splanchnotomy on the Same Side</i>					
7	3.07	4.2 (0.27)†	3 (0)	2.7 (0.37)	3
14	4.09	5.6 (0.37)	4.6 (0.51)	3.7 (0.6)	10
21	2.89	4.8 (1.11)	3.2 (0.31)	3.3 (1.1)	14
28	3.44	5.5 (1.10)	4 (0.56)	3.9 (1.29)	16
56	3.25	5.5 (1.34)	4.1 (0.85)	3.7 (1.23)	20

(From Hinman, F., and Hepler, A.: Arch. Surg. 11: 578, 1925.)

*The figures in parenthesis indicate the actual increase in size of the kidney. They are obtained by proportioning the weight of the animal and the measurements to those of a normal rabbit weighing 2.5 kg., whose left kidney is 3.2 cm. deep and 1.9 cm. wide.

†The figures in parenthesis indicate the actual increase in size when the measurements are proportioned to the animal's weight, using as a normal standard a rabbit weighing 2.5 kg., whose left kidney is 3.2 cm. long, 2.5 cm. deep, and 1.9 cm. wide.

development of hydronephrosis. What unilateral oliguria per se would do has so far been beyond experimental tests.

CONCLUSION

The structural and functional changes occurring in hydronephrosis have never been correlated. No one knows whether or not the activity of a kidney with complete obstruction of its ureter is similar to that of one with a comparable degree of hydronephrotic atrophy following partial ureteral obstruction.

REFERENCES

- Aschoff, L.: Cited by Israel, James and Israel, Wilhelm: *Chirurgie der Niere und des Harnleiters*, Leipsic, 1925, Georg Thieme.
- Fuchs, F.: Die physiologische Rolle des Fornixapparates, *Ztschr. f. urol. Chir. u. Gynäk.* 42: 80-100, 1936.
- Fuchs, F., and Popper, H.: Ueber die Gewebsspalten der Niere, *Virehows Arch. f. path. Anat.* 299: 203-218, 1937.
- Fuchs, F., and Popper, H.: Blut- und Saftströmung in der Niere, *Ergebn. d. inn. Med. u. Kinderh.* 54: 1-75, 1938.
- Fuchs, F.: *The Flow of Water Through the Kidney*, New York, 1944, Manhattan Printing Co.
- Guyon, F., and Albarran, J.: Cited by Israel, James, and Israel, Wilhelm: *Chirurgie der Niere und des Harnleiters*, Leipsic, 1925, Georg Thieme, p. 200.
- Hinman, F.: Hydronephrosis, I. The Structural Changes, *SURGERY* 1945.
- Hinman, F., and Hepler, A. B.: Experimental Hydronephrosis: The Effect of Changes in Blood Pressure and Blood Flow on Its Rate of Development. I Splanchnotomy: Increased Intrarenal Blood Pressure and Flow; Diuresis, *Arch. Surg.* 11: 573-585, 1925; II. Partial Obstruction of the Renal Artery; Diminished Blood Flow; Diminished Intrarenal Pressure and Oliguria, *Ibid.* 649-659; III. Partial Obstruction of the Renal Vein Without and With Ligation of All Collateral Veins, *Ibid.* 917-932.
- Hinman, F., and Lee-Brown, R. K.: Pyelovenous Backflow; Its Relation to Pelvic Reabsorption, to Hydronephrosis and to Accidents of Pyelography, *J. A. M. A.* 82: 607-613, 1924.
- Hinman, F., and Vecki, M.: Pyelovenous Backflow; The Fate of Phenolsulfonphthalein in a Normal Renal Pelvis With the Ureter Tied, *J. Urol.* 15: 267-271, 1926.
- Küster, K.: *Die Chirurgie der Nieren, der Harnleiter und der Nebennieren*, Stuttgart, 1896-1902, Ferdinand Enke.
- Levy, S. E., Mason, M. F., Harrison, T. R., and Blalock, A.: The Effects of Ureteral Occlusion on the Blood Flow and Oxygen Consumption of the Kidneys of Unanesthetized Dogs, *SURGERY* 1: 238-242, 1937.
- Martineau: Cited by Morris, H. in: *Surgical Diseases of the Kidney and Ureter*, vol. I, London, 1901, Cassell & Co., Ltd., p. 398.
- Morris, H.: *Surgical Diseases of the Kidney and Ureter*, London, 1900, Cassell & Co., Ltd.

- Narath, P. A.: *The Hydromechanics of the Calyx Renalis*, J. Urol. 43: 145-176, 1910.
- Rayer, P.: *Traité des maladies des reins*, Paris, 1841, J. B. Baillière et fils.
- Richards, A. N.: *Direct Observations of Change in Function of Renal Tubule Caused by Certain Poisons*, Tr. A. Am. Physicians 44: 64-67, 1929.
- Roberts, W.: *Practical Treatise on Urinary and Renal Diseases*, London, 1896, Smith, Elder & Co.
- Rokitansky, Carl: Cited by Israel, James and Israel, Wilhelm: *Chirurgie der Niere und des Harnleiters*, Leipzig, 1925, Georg Thieme, p. 200.
- Strong, K. C.: *Plastic Studies in Abnormal Renal Architecture: V. The Parenchymal Alterations in Experimental Hydronephrosis*, Arch. Path. 29: 77-119, 1940.
- Winton, F. R.: *Physical Factors Involved in the Activities of the Mammalian Kidney*, Physiol. Rev. 17: 408-435, 1937.

HYDRONEPHROSIS

III. HYDRONEPHROSIS AND HYPERTENSION

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HYPERTENSION has two possible connections with hydronephrosis. Sometimes it might be an accelerator, at other times, an effect. The experiments on the flow of blood and on general hypertension (brain operations, etc.) indicate, however, that hypertension does not increase the rate of progress of hydronephrotic atrophy, a conclusion supported by clinical studies. Hydronephrosis develops in patients with essential hypertension according to rule and in no way differently from its development in other patients. High blood pressure has no influence upon the mechanics of hydronephrosis.

The changes of hydronephrosis, however, could well have an effect on blood pressure. The factors supposedly responsible for hydronephrotic atrophy could act to promote renal hypertension. Renal ischemia, however, is not the essential factor, as was formerly thought. In fact, it is not yet known how constriction of a renal artery causes hypertension. Furthermore, the experimental investigations on the effect of ureteral ligation on blood pressure are mostly negative. All attempts (Hartwich, 1930; Megibow and others, 1940, 1942) to produce permanent hypertension by the simple ligation of one ureter have been unsuccessful. Clinically, also, hypertension is uncommon in simple hydronephrosis. It is an unexpected complication. The same causes of renal hypertension supposedly present in other pathologic conditions, such as atrophic pyelonephritis for example, occasionally occur with hydronephrosis also; but apparently, however, they do not occur in a way so connected with the mechanism of simple hydronephrotic atrophy as always to produce hypertension. Nephrectomy performed for unilateral atrophic pyelonephritis brought the blood pressure to normal in six of ten patients of Nesbit and Ratliff, but in only seven of seventy-six patients of Weiss and Chasis, 1943. It is seen that the renal origin of hypertension is very uncertain.

Renal hypertension appears to depend upon the ratio of ischemic to normal kidney tissue. In hydronephrosis both of these factors are affected. The initiating process is a rise in ureteral and intratubular pressure which decreases renal blood flow and therefore may produce true renal ischemia. Of course, the other modifica-

tions in renal blood flow which occur in renal artery ligation are also produced to some extent in hydronephrosis. The amount of renal ischemia varies with the duration and intensity of the decreased blood flow. The increased intratubular pressure also results in a certain amount of hydronephrotic atrophy of the normal renal parenchyma. The magnitude and course of the resulting hypertension depends upon these two factors as well as the compensatory increase in normal renal tissue in the opposite kidney. This phenomenon of contralateral compensatory renal hypertrophy explains the occurrence of transitory hypertension in unilateral hydronephrosis. Thus, two fundamental processes advance simultaneously in the same kidney to increase the amount of ischemic and to decrease the amount of normal renal substance. Just as in renal arterial constriction, so it is possible that in hydronephrosis, renal excretory insufficiency may develop without the occurrence of hypertension if the decrease in normal parenchyma is inordinately greater than the amount of ischemic renal tissue. In such an event the process leads primarily to destruction of normal kidney tissue, and this may become great enough to simulate complete nephrectomy. (Megibow, Katz, and Rodbard, 1912.)

The foregoing considerations give little encouragement for the cure, by means of nephrectomy, of hypertension occurring in unilateral hydronephrosis. Only a few cases have been reported (Nesbit and Raliff, three patients, aged 37, 24, and 20 years; Bartels and Leadbetter, one patient). This knowledge might encourage the so-called conservative surgery of hydronephrosis, that is an attempt to repair every kidney not entirely destroyed. In addition to the argument of common sense against such a policy, however, there is a real danger that the surgical repair will itself so alter the mediators of blood pressure as to cause hypertension later on. Why this should occur is obscure but the report of Case 1 is an example.

CASE 1.—A 20-year-old carpenter had a successful Y-plastic repair and nephropexy of an uninfected left hydronephrotic kidney, Feb. 27, 1935. After operation the urine remained clear and uninfected, and the patient did well for five years. In 1940, he began to have headaches and nausea. The blood pressure, April 15, 1940, was 160/100; Nov. 3, 1940, lying, 178/116; sitting, 180/116; standing, 174/114; and Jan. 20, 1941, 194/96; 200/122; 192/118. The relative function (the urine from both sides was clear and negative microscopically) on the right side was $17 + 5 = 22$ per cent and on the left (repaired) side, $5 + 2 = 7$ per cent, or essentially the same as in 1935 both before and after the plastic operation. There was no urinary infection and no history of it. Left nephrectomy was done, Jan. 23, 1941. Two days later blood pressure was 170/110; Jan. 31, 1941, one week after operation, it was 130/84, and Jan. 20, 1944, two years later, it was 130/82; the patient had remained continuously well. Fig. 1 shows the kidney and Fig. 2, a microscopic section of it. The patient was last seen Nov. 15, 1944, and at that time was well.

As might be expected, hypertension is somewhat more common in the presence of bilateral hydronephrosis. Comparison of the blood pressures of nine rats "with spontaneous hydronephrosis" with those of 1,207 normal rats showed that all four of those with bilateral and three of the five with unilateral hydronephrosis had hypertension also (Williams, Wegria, and Harrison, 1938). The age of the patient may be a factor in the incidence of hypertension in both unilateral and bilateral hydronephrosis. Compensatory hypertrophy is much less marked in older people, and is almost absent in the bilateral condition. Perhaps Wakerlin is right in saying, "only future work can determine whether essential hypertension is a generic classification one group of which may be of renal origin."

In 260 cases of hydronephrosis at the University Hospital from 1937 to 1941, inclusive, 212 patients had normal blood pressures and 48 had hyperten-

sion. Of the 212 patients, 162 had unilateral and 50, or 23.5 per cent, had bilateral hydronephrosis. Of those with hypertension, 30 had unilateral and 18, or 37.5 per cent, had bilateral hydronephrosis. The ages of those in the



METRIC 1 2 3 4 5 6 7 8 9 10 11 12

Fig 1—Renal hypertension. Photograph of the kidney removed five years after the plastic ureteropelvic repair of a hydronephrosis because the patient suddenly developed renal hypertension.



Fig 2—Photomicrograph from the specimen shown in Fig 1, showing some interstitial fibrosis and some epithelial atrophy in convoluted tubules. The glomeruli are large. So slight is the evidence of inflammation that a complicating atrophic pyelonephritis would not seem to have been the factor in the onset of the hypertension. Furthermore, there had been no loss of function before nephrectomy, and the bladder urine had been continuously free from infection for five years.

bilateral groups are shown in Table I. Twenty-two of the patients with hypertension and unilateral hydronephrosis were operated on with results as shown in Table II.*

*I wish to acknowledge my debt to Lieutenant H. L. Harrington, Medical Co. U. S. N. R. for his thorough compilation of the hospital records.

TABLE I

	WITH NORMAL PRESSURE	WITH HYPERTENSION
Under 20	2	3
20 to 54	37	8
55 to 64	8	3
65 and over	3	4
Total	50	18

TABLE II. RESULTS OF OPERATION IN TWENTY-TWO PATIENTS WITH HYPERTENSION AND UNILATERAL HYDRONEPHROSIS

NUMBER OF PATIENTS	OPERATION	RESULT			
		HYPERTENSION UNAFFECTED	HYPERTENSION REDUCED	NO RECORD	DIED
9	Nephrectomy	5	1	1	2†
3	Plastic repair	3			
5	Lithotomy	2		3	
3	Prostatectomy	1	1		1‡
1	Accouchement		1		
1	Bilateral splachnotomy	1			
22		12	3	4	3

*Large left hydronephrosis due to impacted stone in ureter; left nephrectomy; blood pressure before, 154/90 to 160/91, after, 110/70 to 138/84. Woman, 51 years old and very nervous.

†One from embolism and one from bronchopneumonia.

‡Ten days after transurethral resection there was cardiac failure.

Only one of nine patients had a reduction of blood pressure following nephrectomy for unilateral hydronephrosis and it is doubtful that the operation had a direct relationship to the reduction in this one patient.

Compensatory hypertrophy is a change of pathogenic significance in hydronephrosis and also perhaps in hypertension. Like all glands the kidneys have a reserve power of function which takes care of the many demands of overwork. The ordinary periods of such hyperactivity produce no structural changes. If they are prolonged, however, certain components of the glomerulo-tubule undergo hypertrophy. Glomerular and convoluted tubular parts of the unit enlarge under increased stimulation. Medullary loops and collecting ducts change little. Unilateral ligation of the ureter is followed by compensatory hypertrophy of the opposite kidney just as in unilateral nephrectomy, and this compensatory hypertrophy is no different from that which follows ureteroduodenostomy or an ureterovenous fistula (Rodbard and Katz). Only in these two latter instances the useless kidney, the urine from which is poured back into the circulation, hypertrophies at first to the same degree as its compensatory mate. Hydronephrotic kidneys, therefore, receive the same overstimulation as their compensatory mates. This is the reason that some units, during certain stages of hydronephrotic atrophy, show hypertrophy or, at least, are kept more active and resistant. It is also reason for the rarity of hypertension with hydronephrosis. Furthermore, it explains in part the failure of some hydronephroses to progress. Maatz found five such "stationary" hydronephroses among thirty-two studied. This overstimulation of a hydronephrosis will disappear, however, when the mate has fully compensated by hypertrophy to carry the overload.

CONCLUSION

Hypertension does not increase the rate of progress of hydronephrotic atrophy.

Hydronephrosis rarely causes hypertension.

The later changes in a kidney which has been repaired for hydronephrosis may cause hypertension.

An important factor in the incidence of renal hypertension is the degree of compensatory hypertrophy.

REFERENCES

- Bartels, E. C., and Leadbetter, W. F.: Hypertension Associated With Unilateral Noninfected Hydronephrosis Treated by Nephrectomy, *Lahey Clin. Bull.* 1: 17-20, 1940.
- Hartwich, A.: Der Blutdruck bei experimenteller Uriämie und partieller Nierenausscheidung, *Ztschr. f. d. ges. exper. Med.* 69: 462-481, 1930.
- Maatz, R.: Das "guterhaltene" Nierengewebe in Hydronephrosen, *Zentralbl. f. Chir.* 68: 108-118, 1941.
- Megibow, R. S., Friedberg, L., Rodbard, S., and Katz, L. N.: Changes in Arterial Pressure After Bilateral Complete or Partial Ureteral Occlusion, *Proc. Soc. Exper. Biol. & Med.* 43: 245-248, 1940.
- Megibow, R. S., Katz, L. N., and Rodbard, S.: The Mechanism of Arterial Hypertension in Experimental Hydronephrosis, *Am. J. M. Sc.* 204: 340-350, 1942.
- Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated With Unilateral Renal Disease, *J. A. M. A.* 116: 194-199, 1941; Hypertension Associated With Unilateral Nephropathy, *J. Urol.* 43: 427-447, 1940.
- Rodbard, S., and Katz, L. N.: The Role of Renal Metabolism in Hypertension and Uremia, *J. Exper. Med.* 73: 357-364, 1941.
- Strong, K. C.: Plastic Studies in Abnormal Renal Architecture; V. Parenchymal Alterations in Experimental Hydronephrosis, *Arch. Path.* 29: 77-119, 1940.
- Wakerlin, G. E.: Unilateral Nephrectomy and Hypertension, *J. A. M. A.* 123: 720, 1943.
- Weiss, E., and Chasis, H.: Failure of Nephrectomy to Influence Hypertension in Unilateral Kidney Disease, *J. A. M. A.* 123: 277-279, 1943.
- Williams, J. R. Jr., Wegria, R., and Harrison, T. R.: Relation of Renal Pressor Substance to Hypertension of Hydronephrotic Rats, *Arch. Int. Med.* 62: 805-812, 1938.

THE PRINCIPLE OF EXCISION AND DISSECTION IN CONTINUITY FOR PRIMARY AND METASTATIC MELANOMA OF THE SKIN

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THE only proper treatment for malignant melanoma of the skin is wide surgical excision. This tumor possesses such a degree of radio-resistance, that x-ray and radium should never be employed in treatment as long as the tumor remains in an operable stage. The melanoma is as resistant as the skin which contains it; cauterizing doses of irradiation are necessary to destroy even the primary tumor and for this purpose x-ray and radium hold no advantage over any other form of cautery. We prefer wide surgical removal by sharp dissection. It should be possible in those instances in which the malignant melanoma has not yet metastasized to effect a cure, providing local surgical removal is radical enough in its scope. Unfortunately, the true nature of the disease is often unrecognized by the surgeon, so that a most conservative removal is first employed under the incorrect assumption that a benign nevus is being removed. An early local recurrence is the rule in such instances. The frequency of this occurrence has often led to an incorrect appreciation of the importance of removing premalignant pigmented nevi. When a pigmented mole is completely removed it never recurs as malignant melanoma. The reason this paradox is thought so often to occur is that a malignant change has already occurred in the nevus at the time the patient presents himself for treatment; in fact, this

change is often the reason for the patient's decision to consult a physician. Such changes as a slight increase in pigmentation, ulceration, increased rate of growth, tenderness, bleeding, or change in color may induce the patient to seek surgical consultation.

The average patient with malignant melanoma who applies to the Memorial Hospital has already had a conservative local operation for the disease. If the melanoma is situated on the trunk, thigh, or upper arm, it is sometimes possible to remove it with sacrifice of a very large segment of skin and still effect primary closure of the wound without skin grafting. This is done by dissecting the skin flaps back widely on either side and making the incision relatively long. The removal of a liberal segment of skin containing the tumor with a wide dissection of subcutaneous tissues and deep fascia overlying the muscles may make it possible to give sufficient relaxation so that the wound margins can be approximated under tension without grafting. It is the rule, however, on the mixed tumor service, that all malignant melanomas situated on the hands, feet, lower legs, forearms, and head and neck are to be removed with such wide sacrifice of skin that grafting becomes necessary. In the case of the face it may be possible to restore the defect by some plastic procedure such as sliding or transposed flaps. The constant observance of this rule has caused our surgeons never to be tempted to do less of an operation than one sufficiently radical for removal of a primary melanoma. Within certain limits it is not much more difficult to skin graft a large wound than it is a small one. Therefore, there is no inducement for the more conservative excision. If the melanoma metastasizes by way of the blood stream to the viscera, then all hope of cure by any method must be abandoned. But if the melanoma metastasizes via the lymphatics to regional lymph nodes it is still possible to plan a surgical procedure which will remove both the primary melanoma and the secondary manifestation of the disease in the regional lymph nodes and give the patient an opportunity for survival. In the past several years we have consistently planned each operation for melanoma to include en masse both the primary and metastatic tumors by the procedure which we refer to as excision and dissection in continuity.

THE PRINCIPLE OF EXCISION AND DISSECTION IN CONTINUITY

The first well-planned operation for cancer was conceived independently by William Halsted and Willy Meyer for carcinoma of the breast. No surgical principle to date has been more important than the one conceived for radical mastectomy because this operation allows for the removal of the primary cancer, the secondary deposits of the cancer in regional lymph nodes, namely, the axilla, and the intervening lymphatics en masse. The wide scope of fascial removal and the radical sacrifice of skin intervening between the breast and the axilla ensures, as far as is surgically possible, a complete removal of the primary cancer and the first relay in its metastasis.

Sir Ernest Miles, in his conception of the radical operation for cancer of the rectum in 1908, applied the same principle. The abdominoperineal rectal resection by the classical technique of Miles included removal of the pelvic colon, the rectum, the anus, the mesentery of the colon, and all of the perirectal tissues containing the lymph nodes and lymphatics into which rectal cancer first metastasizes by way of the lymph stream. In this instance the operation has not been improved upon and remains the procedure of choice after thirty-five years. There are very few other locations where this principle of excision and dissection in continuity has been successfully applied. Radical vulvectomy for epithe-

liomas of the vulva, as conceived by Bassett, was a step in this direction because it included bilateral groin dissection with removal of the vulva. When this operation is done as a single-stage procedure with removal of the skin of the groin and vulva, and radical dissection of the lymph nodes in both groins, the operation is good indeed because the excised tissue includes not only the primary cancer and the lymph nodes containing possible metastases but the intervening lymphatics and surrounding skin as well.

For cancer of the stomach the principle is too radical to find universal employment at this time, so the majority of gastric cancers are removed by partial gastrectomy. The disadvantages of total gastrectomy are too numerous to be recounted here, but the operation is a feasible one, as has been proved by its adoption for certain advanced gastric cancers which can only be taken care of by this radical procedure. The reason for mentioning total gastrectomy is that the operation can be performed to correspond with the complete procedures as described for the breast, rectum, and vulva, namely, removal of the entire organ including the great omentum and the four major groups of perigastric lymph nodes into which the first relay of lymphatic metastases are deposited.

The operation of excision and dissection in continuity for primary and metastatic tumors cannot be successfully employed for cancers of the oral cavity, pharynx, nasopharynx, and accessory nasal sinuses. The only cancers in this group which can possibly be treated by this principle are certain epitheliomas of the lower lip in which a radical excision of the lower lip together with the skin of the chin may be done and continued down to include a bilateral suprahyoid neck dissection. In this procedure the intervening lymphatics are removed between the primary epithelioma and the lymph nodes into which it metastasizes first. In the case of cancers of the tongue, tonsil, nasopharynx, etc., it is of course possible to obtain cures of the primary tumor and also to control the patient by subsequent neck dissection or radiation therapy of cervical lymph nodes containing metastatic cancer. However, it must be pointed out that in all these situations there are intercalated lymph nodes in the lymphatic pathways between the primary cancers and the main group of cervical nodes; these small nodes may contain metastatic foci of cancer which are not accessible to surgical extirpation. This does not suggest that cure is not possible under these circumstances, but the ideal principle under discussion cannot be applied in tumors of the head and neck, as has been said, except in the case of epitheliomas of the lower lip and of the inferior alveolus when jaw resection is added to neck dissection.

The same surgeon who will invariably perform a radical mastectomy or an abdominoperineal rectal resection for cancers in these locations apparently is content to perform the most limited type of excision for malignant melanoma of the skin. This tumor tends to recur locally with such a high frequency and to metastasize to regional nodes with such a high incidence that it is imperative for every surgeon treating this tumor to realize the extreme importance of applying radical surgical principles in its care. The operation, therefore, should be planned to be as radical as that for other types of cancer. This requires considerable ingenuity because the malignant melanomas are so variable in their location and drain into so many different groups of regional lymph nodes. The treatment of this tumor, therefore, necessitates careful study of the anatomy of the lymphatics of the skin in all parts of the body.

If the melanoma is situated closely adjacent to the group of lymph nodes into which it may metastasize, then the scope of the operation may be so 1 1

as to enable the surgeon to remove the primary melanoma and the regional lymph nodes in one encompassing excision of skin and deeper structures. The procedure entails a wide sacrifice of skin surrounding the melanoma and an extension of this skin excision to include the skin overlying the regional lymph nodes. The skin flaps are then dissected widely back, and in so doing, the subcutaneous tissues are stripped from the skin. The underlying fascia is then removed, together with the specimen from the muscles, and the dissection carried to the lymph node-bearing regions where a meticulous and radical dissection is carried out. Various bizarre-shaped incisions will result, depending on the exact location of the melanoma. As a rule, the wide dissection of the skin and removal of so much subcutaneous fat and fascia will enable the surgeon to approximate the skin margins without employing a skin graft. The excised surgical specimen includes, therefore, in continuity, the primary melanoma, the skin surrounding it, the subcutaneous tissues and fascia containing the lymphatics intervening between the melanoma and the regional lymph nodes, all of the fat, lymphoid, and areolar tissues in the region of the first relay of metastases.

This procedure, of course, is not feasible where a long distance intervenes between the primary tumor and the regional lymph nodes. For example, in the case of the subungual melanoma of the finger or toe with metastasis to the axillary or inguinal lymph nodes, the average surgeon is loath to apply a principle so radical as the removal of the entire limb. The disarticulation of this limb, together with a groin or axillary dissection, is probably the only way of offering the patient the maximal degree of safety. Although we have done this for some patients with conditions suggesting a bad prognosis, it is our usual practice under these circumstances to amputate the finger or the toe and later to do a radical axillary or groin dissection. There is a very great hazard that recurrence of the melanoma may develop in the intervening space between the finger or toe and the axilla or groin; it is not difficult to understand this likelihood and to realize that melanoma cells have been compelled to travel, usually by embolism, the long distance intervening between the digits and the lymph nodes in the axilla or groin. It would not be entirely unexpected to find that some of these cells have lodged somewhere in the intervening lymphatics; their subsequent growth and development seem to be abetted by the lymph stasis which always occurs to some degree after the radical removal of the lymph nodes. If any nodules do develop on the arm or leg following this procedure then nothing short of a disarticulation should be considered.

The operation which we have termed excision and dissection in continuity of primary and metastatic melanomas to regional nodes may be applied for all malignant melanomas situated in the skin draining into the cervical lymph nodes, the axillary lymph nodes, and the inguinal lymph nodes. For example, malignant melanoma involving the skin of the lower half of the face, the lower lip and chin, the upper chest, and the neck may be removed in continuity with a radical neck dissection by the procedure just outlined. Melanomas involving the superior two-thirds of the upper arm, the pectoral region, scapular region, the axillary skin, and the skin in the infra-axillary region may be removed in continuity with a radical axillary dissection by the procedure just described. Melanomas involving the superior two-thirds of the thigh, the skin of the buttocks, or the iliac quadrant of the abdomen may be removed in continuity with the radical groin dissection. Malignant melanomas involving the skin of the anus and the genitals, both male and female, may be removed in continuity

with the lymph nodes in both right and left inguinal regions by a combination excision with bilateral groin dissection. Even under the most advantageous of circumstances in which every precaution is taken by the surgeon, the curability of the disease is, of course, not absolute. For a principle which has found its place so firmly established in the treatment of malignant tumors of other organs it is found that its routine application in the case of the malignant melanoma should be considered, because this tumor is one of the most dangerous in the entire category of neoplastic diseases.

But in the case of melanomas of the inferior extremity, a multiple-stage procedure must usually be worked out. We have found from experience that it is unwise to remove a melanoma or epithelioma of the foot and at the same time dissect the groin even though metastases are evidently present, because even here there may be metastases en route.

It requires a nicety of judgment to decide on the interval of inaction when metastases are known to be present, and even then the wrong decision may be made. Ten to fourteen days at the most are permitted to elapse before the second stage or groin dissection is accomplished. In the past, the primary cancer, for example, a melanoma on the foot, and the lymph nodes in the groin have been removed at a single operative seance only to be followed in too many instances by the appearance of innumerable subcutaneous and intracutaneous nodules along the lymph pathways in the leg or thigh. It is our belief, based on theory substantiated only by personal experience, that the lymph nodes in the groin should remain to exercise their function as catch basins or filters for cancer cells which may be metastasizing at the time the primary cancer is removed. The groin dissection should not be postponed too long, if metastases are clinically evident; otherwise the hazard exists of secondary metastasis to the next higher relay or chain of nodes, too far removed superiorly to be surgically excised.

The interval between the first appearance of the primary lesion and the known recognition of metastasis in lymph nodes of the groin is not the same for all malignant tumors. In the Memorial Hospital series, the interval for epidermoid carcinoma is thirty months, and for malignant melanoma only fifteen months, which is in agreement with the usual greater degree of malignancy and the more rapid growth of melanoma. At the two extremes, there is one case report of an instance in which metastasis in the inguinal nodes appeared twelve years after an epithelioma of the foot had been treated and other examples of the simultaneous discovery by the patient of a primary melanoma of the clitoris or vulva and enlarged inguinal nodes, obviously the site of metastatic deposit. The delayed enlargement of these nodes after a lapse of several years indicates that metastases had been present all the time but remained dormant or latent for some unexplainable reason.

ELECTIVE GROIN DISSECTION

The caption "elective" is a misnomer that is used here for want of a better term. The operation called by this name refers to the elective removal of lymph nodes in the groin even though they are not palpable and there is no clinical evidence of metastases being present. It is our opinion that this dissection should be done routinely for all melanomas of the extremity and genitals. In a group of seven dissections of this type for melanomas of the lower extremity, two of the patients were found to have microscopically identifiable melanoma in the inguinal lymph nodes even though the surgeon at the time of

operation found no gross evidence of involvement. In another group of ten similar axillary dissections for melanoma of the upper extremities, five, or 50 per cent, of the series showed microscopic evidence of metastases to the lymph nodes even though there was no gross evidence determinable preoperatively or during the course of the operation. It is our contention that this early operation, although needlessly done in some instances, affords the patient with metastatic melanoma in the groin a better and earlier opportunity of cure. It seems reasonable that the fewer lymph nodes involved and the earlier the involvement, the better will be the prognosis. In the case of epidermoid carcinoma, occurring in the lower extremities, this routine dissection is never performed, as one waits until there is evidence of involvement. The reason is that this type of cancer does not so frequently metastasize to inguinal nodes and there is a natural wish to avoid unnecessary operations of this major character. For epitheliomas of the scrotum and vulva, however, it is our belief that the bilateral inguinal dissection is constantly indicated, even in the absence of palpably enlarged lymph nodes.

There is no urgency in doing this groin dissection as an elective procedure, as we have shown that an average time of fifteen months elapses from the time the primary melanoma is recognized before metastasis in inguinal nodes are apparent. As a rule, six weeks are permitted to elapse after the primary melanoma has been surgically excised before the second stage or elective groin dissection is done. Patients who refuse this procedure are kept under close and frequent observation. This principle of elective groin dissection is based on a study made several years ago of all malignant tumors of the extremities, which revealed the distressing information that radical dissection of the primary melanoma often was not curative in itself, even in patients in whom no regional lymph nodes were palpable, because a considerable number of these patients would return during the observational period with large confluent nodes containing metastatic melanomas which were not observed at the previous visit.

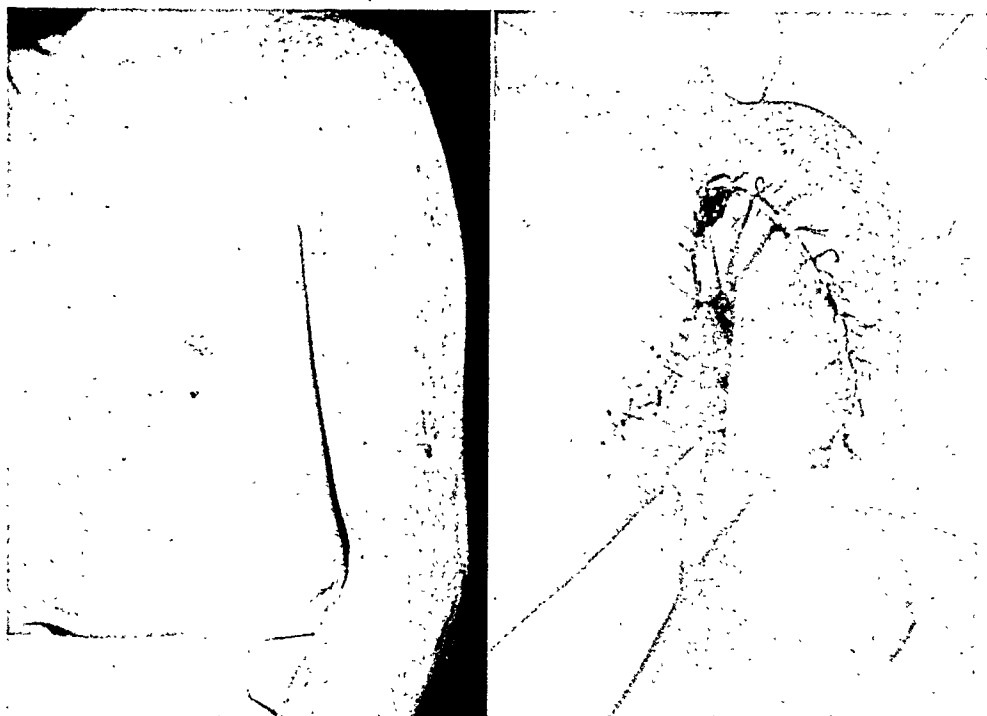
CASE REPORTS

CASE 1.—J. G., a 39-year-old white man, had long been aware of the presence of a flat pigmented mole, minute in size, involving the skin of the left upper arm, but because of a slight itching and bleeding of a month's duration a physician electrodesiccated this supposed nevus about fifteen months prior to the patient's application to the Memorial Hospital. One year later a small nodule was felt close to the insertion of the left pectoralis major muscle. It was surgically removed through a small incision at another institution; under the microscope it was found to be metastatic melanoma in a small lymph node.

Physical Examination: On admission to the Memorial Hospital a flat thin scar was noted on the anterolateral aspect of the left upper arm a short distance above the elbow. It was approximately the size of the usual vaccination scar. A small, macular, pigmented spot was observed on one margin of the scar, but there was no palpable tumor. There were no significantly enlarged lymph nodes in the left axilla. A roentgenogram of the chest revealed no evidence of pulmonary metastasis.

Diagnosis.—Malignant melanoma of the skin of the arm with metastasis to the axillary lymph nodes.

Treatment.—Because the operative scars from the procedure performed on the primary melanoma and the metastatic melanoma in the regional lymph nodes were so small, it was decided to perform a more radical surgical excision of the primary site of the melanoma. This was done by making an elliptical incision through the skin from a site below the original scar to include a wide segment of skin surrounding this scar and extending up to the anterior aspect of the arm in such a way as to include the skin of the axilla. The skin flaps were dissected widely back and the fascia over at least 50 per cent of the circumference of the arm and anterior shoulder were removed, together with all of the axillary contents.



A.

B.



C.

Fig. 1 (Case 1).—Malignant melanoma of skin of arm. A, Photograph on admission. Scar following electrodesiccation of melanoma in skin of left upper arm above elbow, and scar of excision of small lymph node which contains metastatic melanoma. B, Photograph of surgical wound, showing extent of operation. Note tightness of wound due to great sacrifice of skin. C, Photograph of healed axillary and arm wound. There is only slight disfiguration and no impairment of motion.

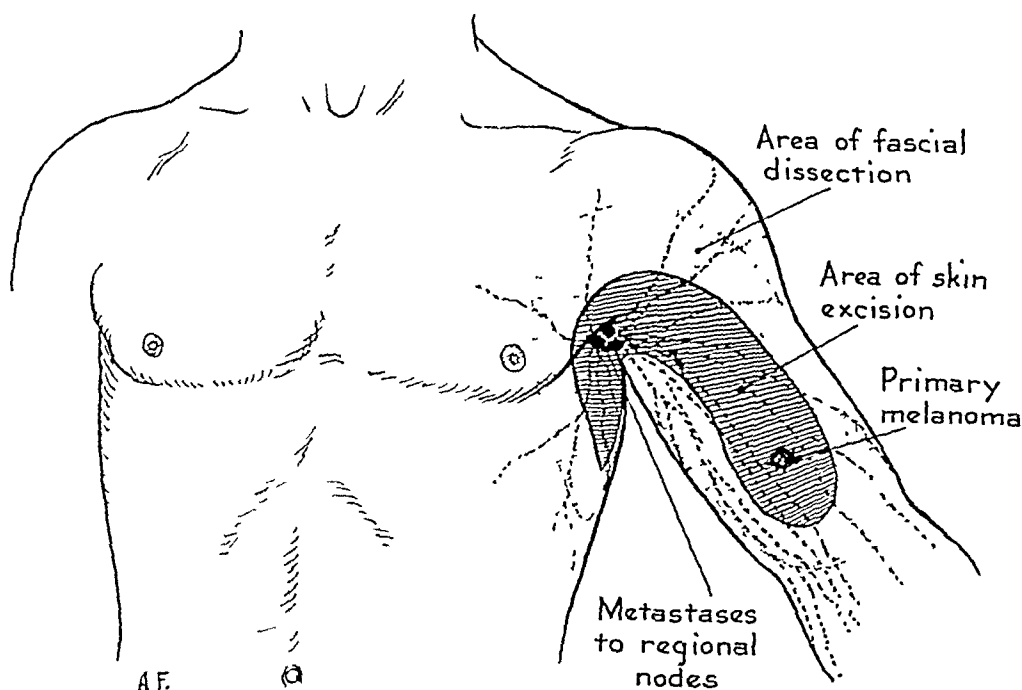


Fig. 2 (Case 1).—To illustrate the principle and scope of the incision and dissection in continuity of a primary melanoma of the arm with metastasis to axillary lymph nodes. The relative amounts of skin and deep fascia removed in this operation are shown.

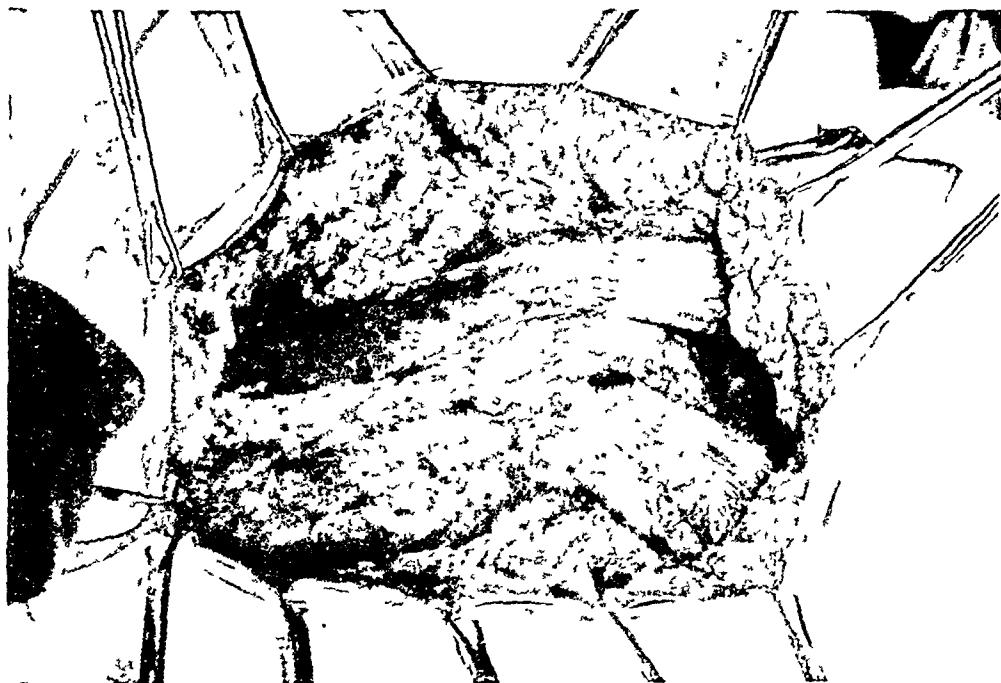


Fig. 3—View at operation in another patient who had a recurrent melanoma on the medial aspect of the right upper arm with metastasis to right axillary lymph nodes. After sacrifice of a continuous and liberal segment of skin, the flaps are dissected widely back to permit the removal of fascia, lymphatics, and the axillary contents.

Because of this great development of skin flaps it was possible to approximate the wound margins and to secure primary wound healing; the wound was under considerable tension, but no skin grafting was necessary.

Pathologic Report.—There was no evidence of recurrent melanoma in the scar where the electrodesiccation had been done; the residual pigment was phagocytized melanin. Numerous axillary lymph nodes contained metastatic melanoma.

CASE 2.—E. R., a 44-year-old white woman, had been aware for five years of the presence of a bluish intracutaneous nodule situated on the left upper anterior chest just below the inner third of the left clavicle. Two and one-half years prior to admission to the Memorial Hospital this nodule increased in size and was surgically removed at another institution. A local recurrence developed within eleven months and a second surgical excision was performed at the same institution. Three months later still another recurrent nodule developed adjacent to the scar of the original excision, and this was also removed. All of these operative procedures were of minor extent, just large enough to encompass the tumor and effect wound closure. The longest incision was only 5 cm. and the underlying fascia had not been removed. Six months before entrance to the Memorial Hospital she observed some enlarged lymph nodes in the left supraclavicular space.

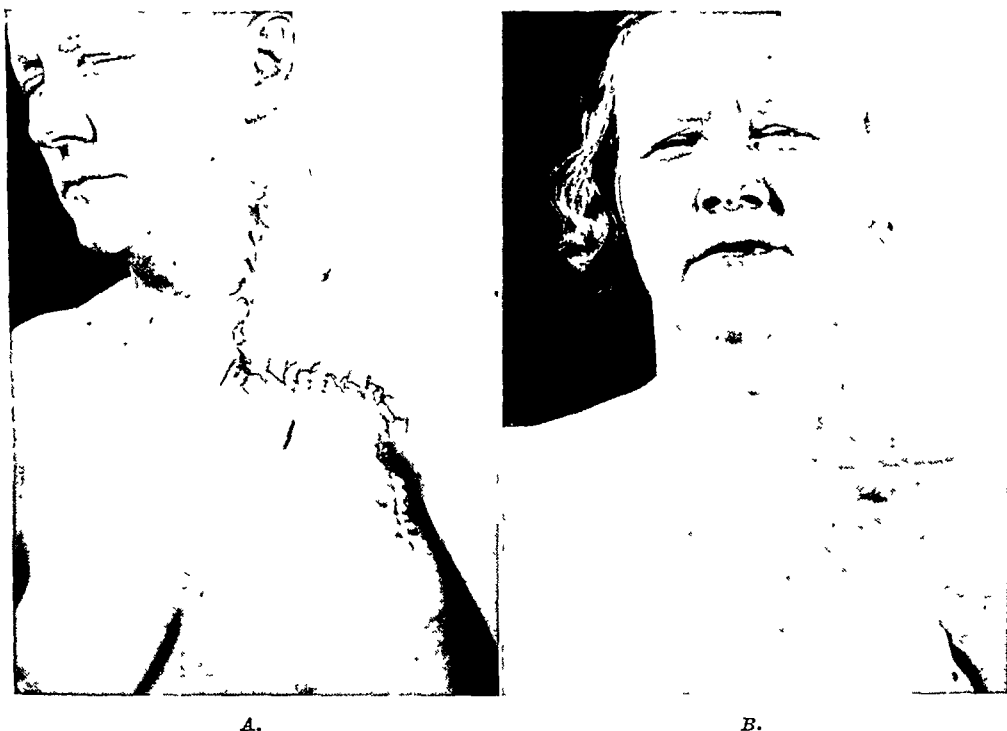


FIG. 4 (Case 2).—A, Combined left supraclavicular and left axillary dissection with excision of a malignant melanoma of the skin in the anterior pectoral region. This melanoma had metastasized to both regional groups of lymph nodes. B, Same patient after healing of the wound.

Physical Examination.—A short linear scar was seen in the skin on the left upper anterior chest wall below the clavicle. There was no evidence of tumor in the immediate region of the scar. There were several large freely movable lymph nodes in the left supraclavicular space extending into the posterior cervical triangle. There were also some discrete, large, firm lymph nodes in the left axilla. The axillary lymph nodes were in the lower and anterior axillary groups; the apical axillary lymph nodes were not clinically enlarged. On aspiration biopsy one of the supraclavicular lymph nodes was reported by Dr. Fred Stewart, the pathologist, as a nonpigmented melanoma. A roentgenogram of the chest revealed no evidence of pulmonary metastasis.

Presumptive Diagnosis.—Melanoma of the skin of the chest with metastasis to the left supraclavicular lymph nodes and left axillary lymph nodes.

Treatment.—The lymphoid metastases from the primary melanoma had evidently appeared in two directions, upward to involve the lymph nodes in the lower neck and laterally,

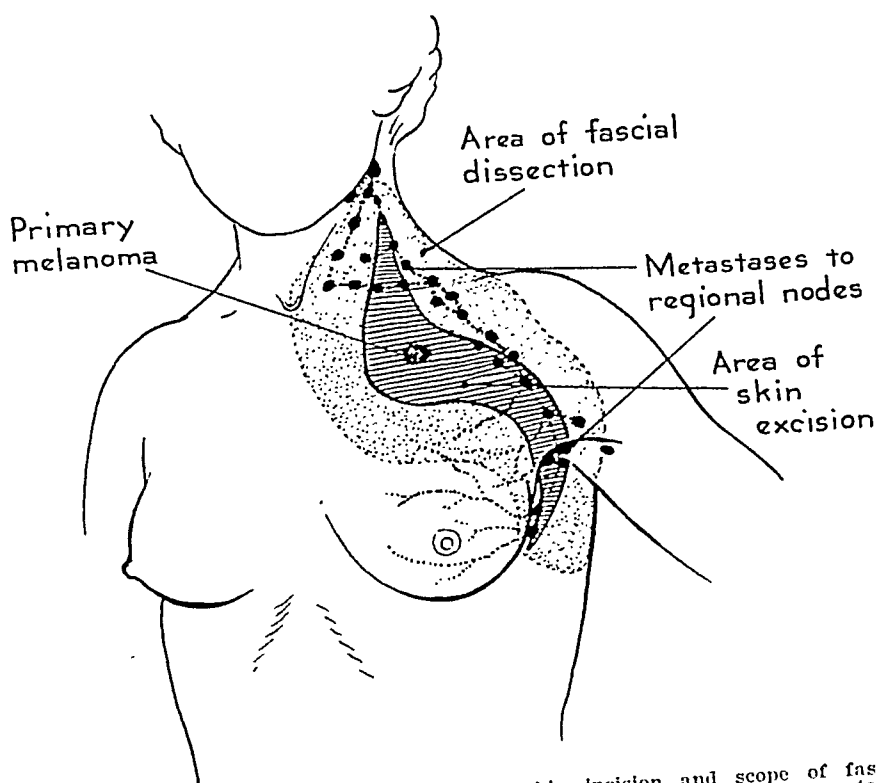


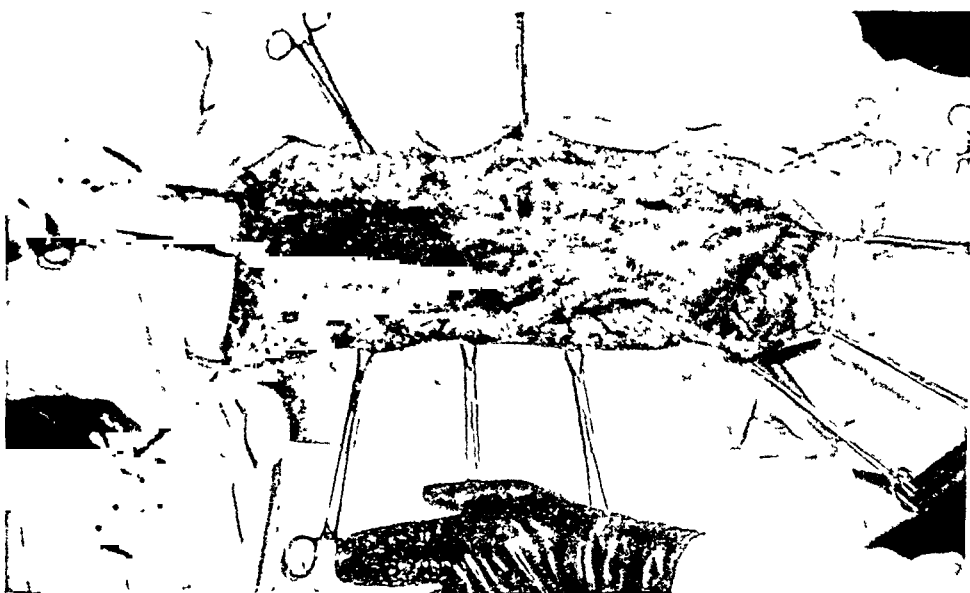
Fig. 5 (Case 2).—To illustrate the planned skin incision and scope of fascial and regional lymph node dissection for a melanoma of the anterior pectoral region metastatic to axillary and supraclavicular nodes.



Fig. 6 A (Case 3).—Malignant melanoma of skin overlying sternum with bilateral axillary metastases. A, Photograph showing location and minute size of primary melanoma.

and downward to drain into the lower axillary lymph nodes. From the distribution of these enlarged nodes it did not seem possible that there was a direct communication or extension through the apex of the axilla to the nodes beneath the clavicle. Therefore, an operation was planned which included a wide removal of the skin of the chest wall in continuity with that of the neck and left axilla. The skin flaps were dissected widely back and the subcutaneous tissues and fascia overlying the pectoral muscles, the clavicle and the lower two-thirds of the left neck as well as the left axilla were surgically removed, together with the underlying lymph nodes. The dissection in the neck was of a radical character and extended as high as the submaxillary and digastric nodes on the left side. Only the lower lymph nodes in the left axilla were found to be involved. The apical and upper groups of nodes were microscopically free of tumor. Because of the development of skin flaps it was possible to approximate the skin margins and thereby effect a primary wound closure. No skin grafting was necessary.

B.



C.

Fig. 6 *B* and *C* (Case 3)—Malignant melanoma of skin overlying sternum with bilateral axillary metastases. *B*, Photograph at operation showing development of skin flaps, plan of incision, scope of fascial removal, and bilateral wound closure. *C*, Primary wound closure.

Pathologic Report.—The lymph nodes in the supraclavicular space axilla were found to be replaced by metastatic melanoma.

CASE 3.—E. R., a 41-year-old white man, stated that a small pigment present since birth on the skin overlying the upper sternum. He insisted it was the same as it had always been according to his knowledge, and at no time any unusual changes. His chief complaint was the presence of lumps in the axilla which he had recently become aware. The family physician suspected the enlarged lymph nodes and referred him to the Memorial Hospital.

Physical Examination.—The patient was a vigorous adult man in good health. Situated in the skin overlying the upper sternum was a small, deeply pigmented lesion. It measured only 1 cm. in diameter; it was nonulcerated and apparently benign. Both axillae contained large, firm discrete lymph nodes.

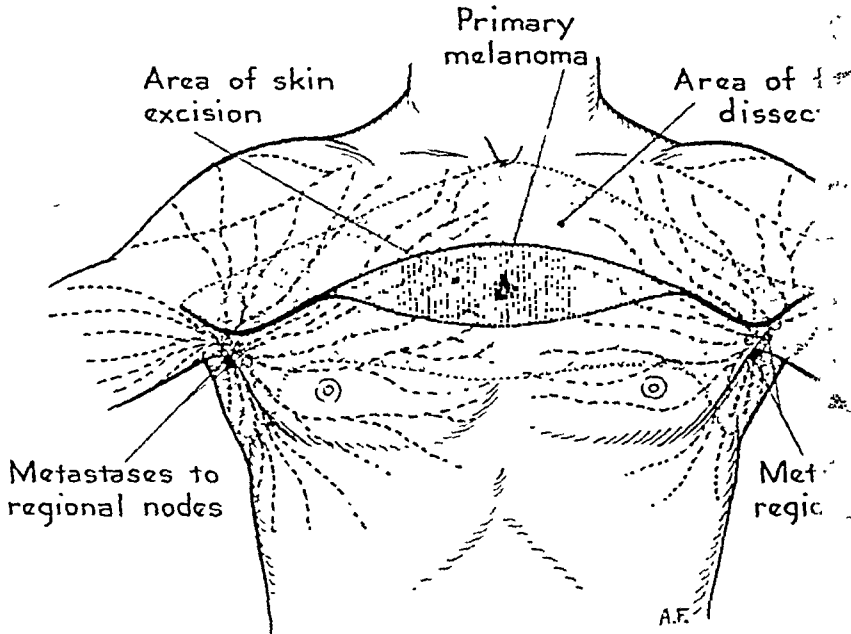


Fig. 7 (Case 3).—To illustrate the length of incision, the comparative and fascia removed, and the general scope of the operation for excision in continuity.

Presumptive Diagnosis.—Melanoma of the skin of the chest wall with metastases.

Treatment.—Because the primary melanoma was situated in the midline anteriorly, and because the lymphatics of this region drain to the axilla and neck, it was decided to perform an excision and dissection in continuity of the melanoma and the bilaterally involved lymph nodes. A wide expanse of skin in an elliptical incision made transversely across the chest wall with the tumor in the center of the excised skin. The incision was extended on either side to include a small portion of the axilla. By retracting the pectoral muscles on each side the axillae were cleared of their lymphoid structures, fat, and areolar contents. The upper flaps were dissected back widely and the subcutaneous tissues over the sternum overlying the pectoral muscles were surgically removed with the specimen. The extent of this fascial dissection can be approximated when it is said that from the substernal notch and level of the clavicles was removed down to the nipples. Because of this great development of skin flaps it was possible to close the skin margins the entire length of the wound, although this was done with caution. Skin grafting therefore was not necessary in this case. Healing occurred without complication. The patient had excellent arm function afterward.

Pathologic Report.—Primary melanoma of the skin of the chest wall with metastases to numerous lymph nodes in both axillary regions.

CASE 4.—E. C., a 60-year-old white man, had been aware "all his life" of a skin lesion in the right lower quadrant of the abdomen on a level with the umbilicus. The lesion was apparently congenital. Two months before applying to the Memorial Hospital he had noticed a change in the size of the lesion.

had observed that this lesion began to increase in size and to exhibit increased pigmentation. Immediately before admission to the institution he observed the presence of a mass in the right groin.

Physical Examination.—A flat brown nonulcerated lesion measuring 1.5 cm. in diameter was seen in the skin of the right side of the abdomen on a level with the umbilicus. There was a group of confluent lymph nodes in the region of the right inguinal and femoral regions. There were no palpable axillary lymph nodes. A roentgenogram of the chest showed no evidence of pulmonary metastasis.

Diagnosis.—Malignant melanoma of the skin of the abdomen with metastasis to the right inguinal and femoral lymph nodes.



Fig. 8 (Case 4).—Primary melanoma of skin of abdominal wall, metastatic to inguinal lymph nodes.

Treatment.—A local excision was made of the tumor on the abdominal wall; this was subjected to microscopic study. The report was malignant melanoma. A very radical surgical procedure was then planned to include the site of the primary tumor and the inguinal and femoral lymph nodes. This included a wide removal of the skin in continuity with the skin of the groin, and a very wide fascial dissection of the right iliac quadrant of the abdomen, together with the fascia and lymph nodes in the right groin. Because of the wide development of the skin flaps it was possible to effect a primary wound closure. No skin grafting was done. The wound healed by primary intention.

Pathologic Report.—Malignant melanoma involving the inguinal and femoral lymph nodes.

CASE 5.—A. K., a 59-year-old man, had been aware of a flat black pigmented skin lesion just above the right nipple which had been present since early childhood. It remained quiescent until two months before his application to the Memorial Hospital. At that time it grew rapidly, became ulcerated and fungating. No previous treatment had been administered other than the application of bland ointment.

Physical Examination.—Examination revealed an elevated, fungating, superficially ulcerated, sessile, reddish tumor measuring 2 cm. in diameter and $3\frac{1}{2}$ cm. in height, situated in the skin on the right anterior chest wall just above and medial to the right nipple. There was a halo of black pigment surrounding the base of the tumor. This lesion was freely movable with no surrounding or satellite nodules. There were no significantly enlarged axillary lymph nodes. A roentgenogram of the chest revealed no evidence of pulmonary metastasis. The presumptive diagnosis was melanoma.

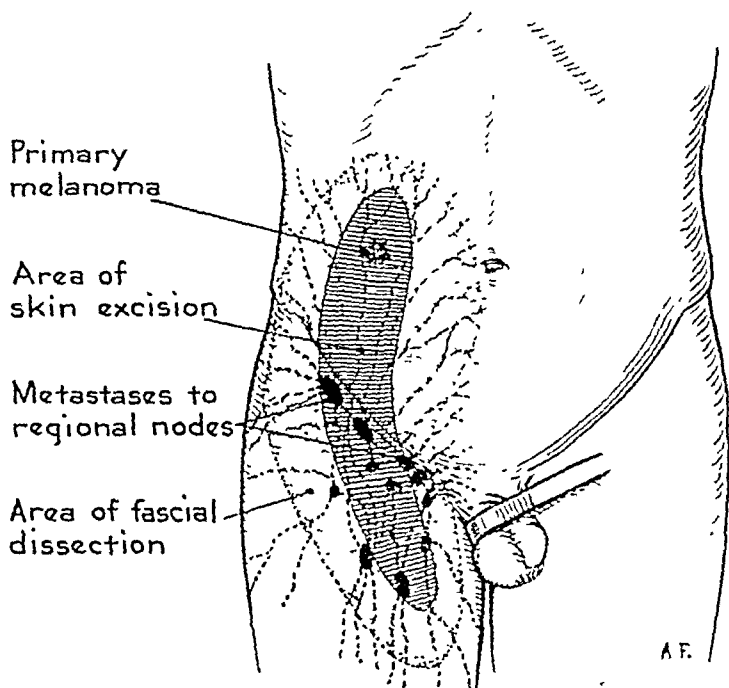
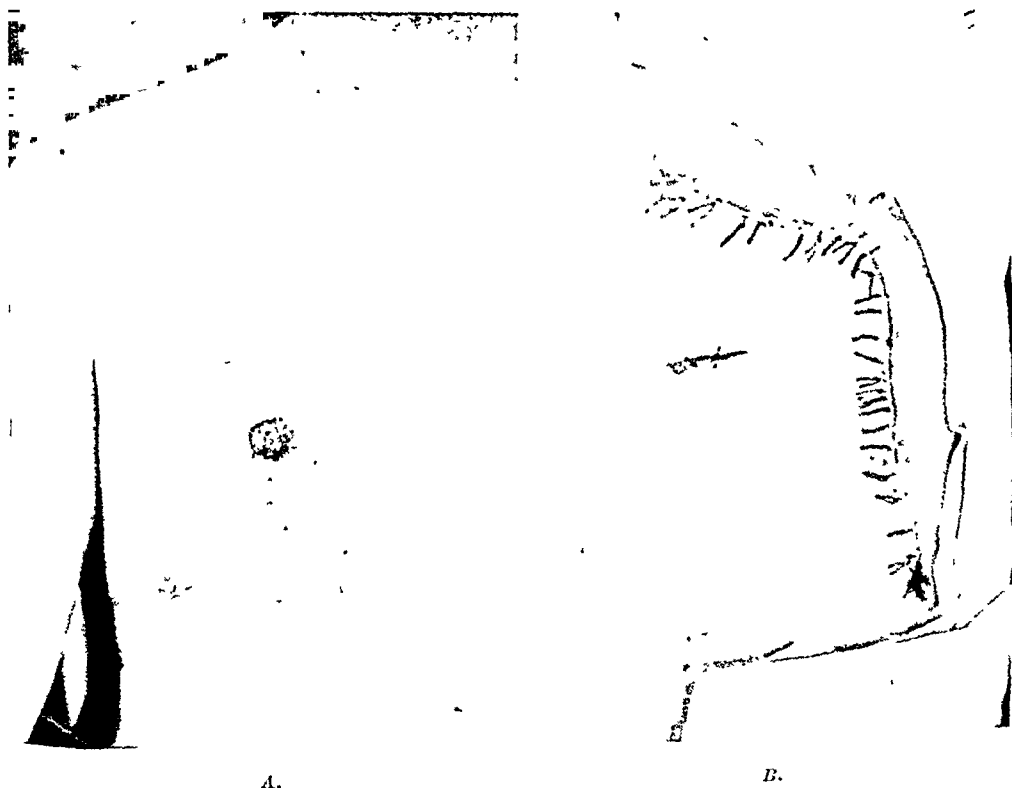


Fig. 9 (Case 4).—To illustrate the scope of operation planned for excision en masse of the primary melanoma of the abdominal wall and the secondary deposits in the inguinal lymph nodes.

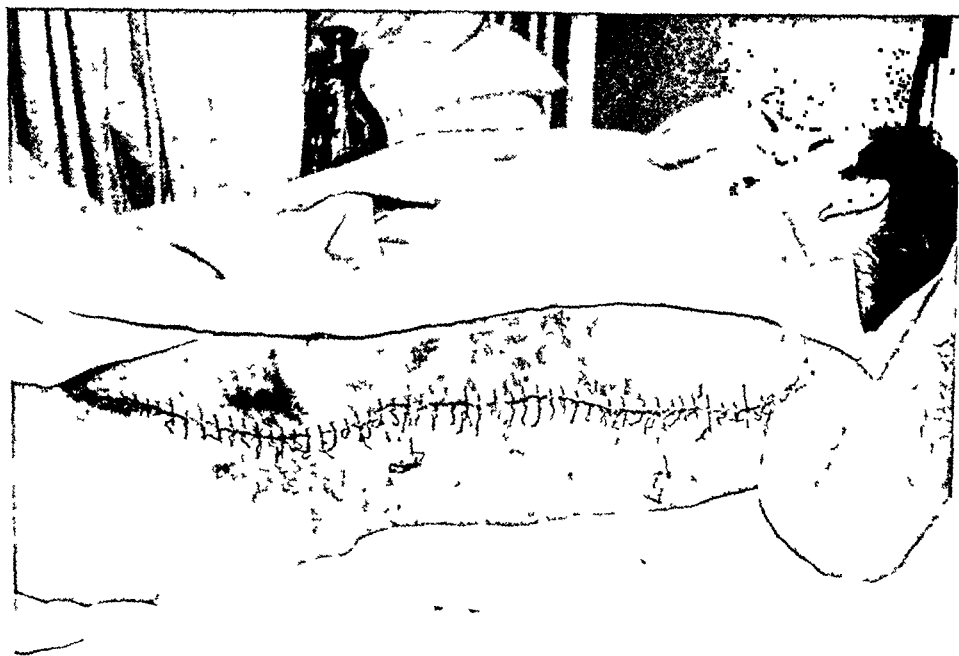
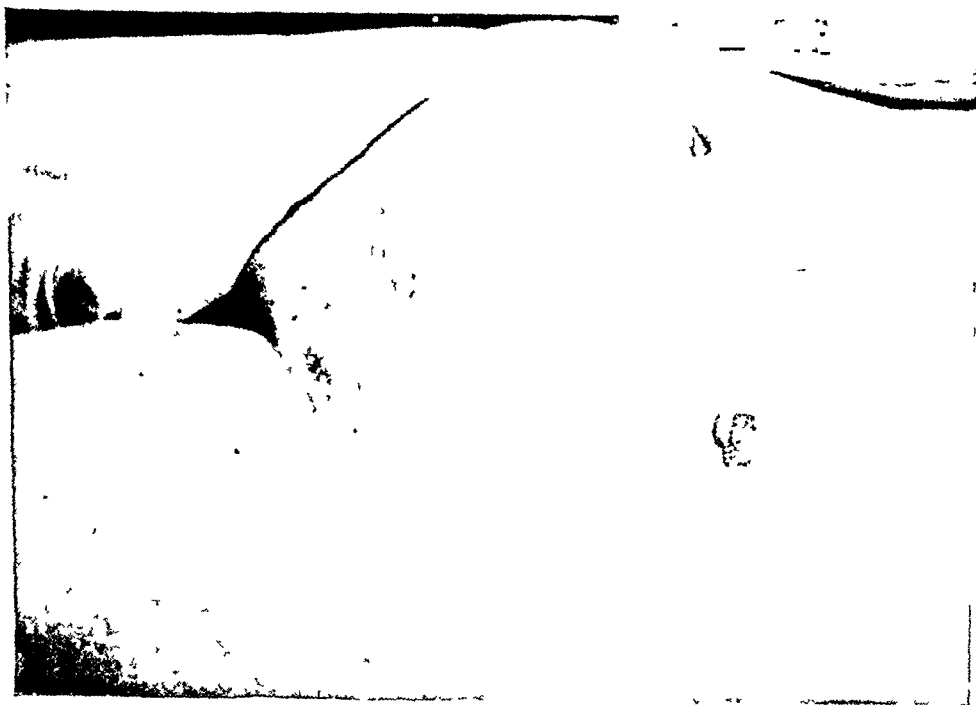


A.

B.

Fig. 10 (Case 5).—A, Primary melanoma in skin of male breast. B, Radical mastectomy by the classical Halsted-Meyer technique. The pectoralis major and minor muscles have been removed. The amount of skin and fascia sacrificed can be judged from the location of the wound and the drains.

A.



B

Fig 11 (Case 6) —A, Primary melanoma in skin of abdominal wall, note enlarged inguinal node. B, Operative wound to show inclusive axillary and inguinal dissections with wide removal of skin and fascia in continuity to encompass the primary melanoma. The extent of the fascial dissection can be seen by the location of the ecchymoses and the drains.

Treatment.—The indications for a radical mastectomy were here as clearly defined as for a carcinoma of the breast. Accordingly, a wide elliptical incision was made from the axillary apex down to the epigastrium encompassing a wide segment of skin. The skin flaps were dissected widely back and the entire breast and nipple, together with the underlying fascia, were removed with the axillary contents. The pectoralis major and minor muscles were removed and the axilla dissected in the customary Halsted-Meyer technique. The fascia over the upper right rectus muscle was removed with the specimen. It was possible to effect a primary closure of the wound without skin grafting.

Pathologic Report.—Malignant melanoma of the skin adjacent to the nipple. The breast proper was not involved. All of the axillary lymph nodes were studied microscopically and none of them was found to contain metastatic melanoma.

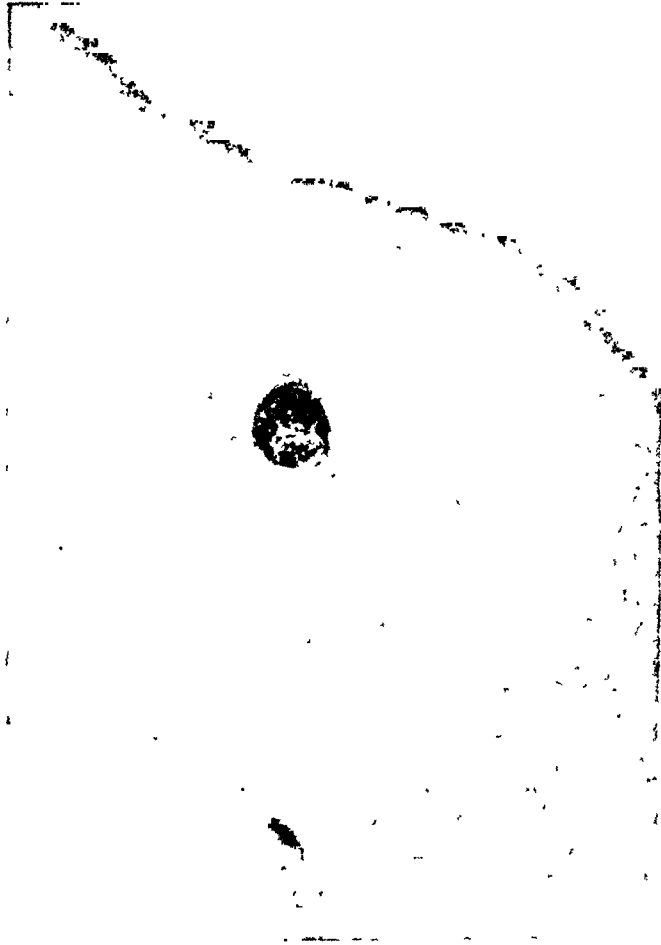
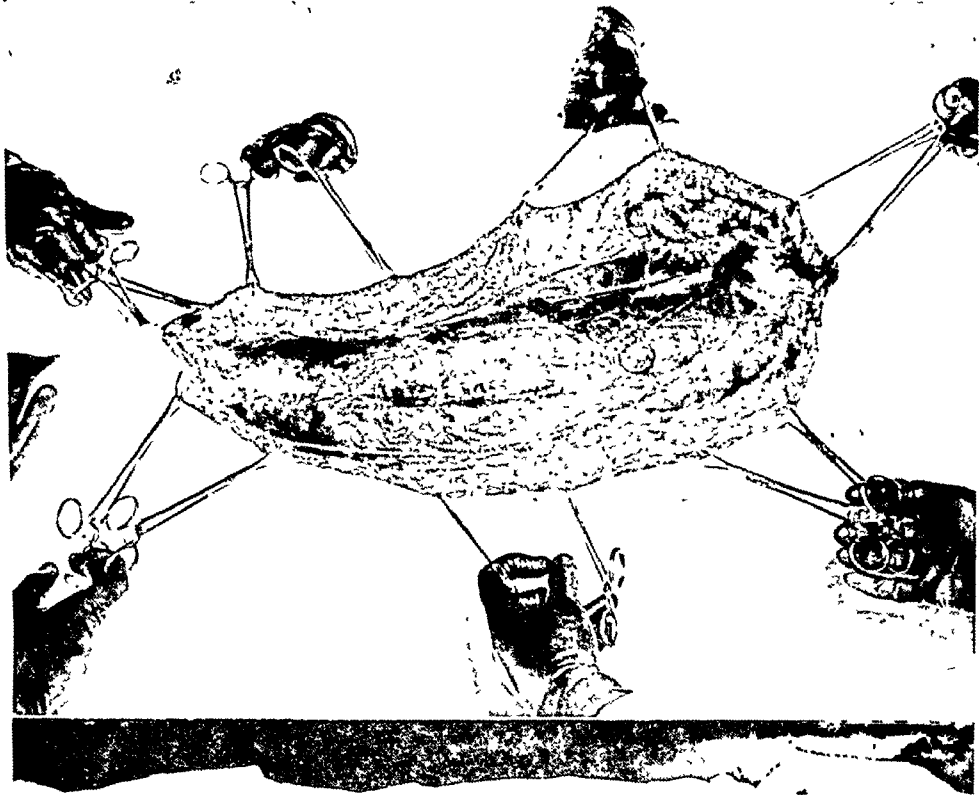


Fig. 12 A—Lesion 1 cm. in diameter situated just above and medial to left knee. History of growth for six months.

CASE 6.—G. F., a 36-year old white man, stated that as long as he could remember he had had a pigmented wartlike lesion involving the skin of the left side of the anterior abdominal wall just at the level where he wore his belt. This lesion was constantly irritated by the belt. Five weeks before application to the Memorial Hospital, he observed a mass in the left groin which gradually increased in size. On questioning, he related that there had been no apparent change in the skin lesion on the abdominal wall except for occasional bleeding, which occurred for the first time six months before. A biopsy made by the family physician was reported as malignant melanoma.

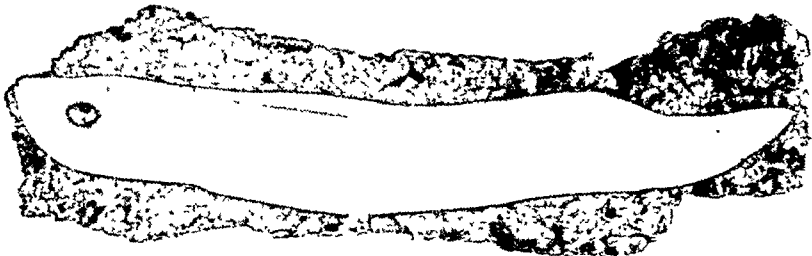
Physical Examination.—On the skin of the left anterior abdominal wall about 12 cm. lateral to the umbilicus and on a level superior to the umbilicus was a papillary grayish-black tumor, sessile in character and measuring 1.5 cm. in its largest diameter. In the left groin one large lymph node could be felt in the superficial inguinal group; the other lymph nodes palpable in the femoral trigone did not seem significant. The liver was not palpable and there was no clinical evidence of metastatic involvement of the left axillary lymph nodes. A roentgenogram of the chest gave no evidence of pulmonary metastasis.



B.



C.



D.

Fig. 12—B, Open wound showing patella, exposed muscles of thigh and split inguinal ligament (with clamps). C, Wound closed with multiple drains. D, Specimen removed tissue showing lesion below and contents of groin above. The fascia is removed from the muscle much more widely than the skin.

Diagnosis.—Malignant melanoma of the skin of the abdominal wall with metastases to the left inguinal lymph nodes.

Treatment.—The skin of the abdominal wall superior to the umbilicus contains lymphatics which drain chiefly to the corresponding axilla. Because of the known presence of metastasis in the left inguinal nodes, the location of the primary melanoma in the skin of the left flank slightly superior to the level of the umbilicus, and the known common route of lymphatic dissemination for malignant skin tumors of this location, a decision was made to apply the principle of excision and dissection in continuity for the primary tumor and regional lymph nodes involved or possibly involved; that is, dissection of the left axilla and left groin, together with the primary tumor. A long elliptical incision was made which included all of the skin between the left axilla and the femoral and inguinal regions, together with a wide strip of abdominal skin encompassing the primary melanoma at its central part. These lateral skin flaps were dissected widely back in the same manner as when a radical mastectomy is performed. The dissection in the left groin included the removal of the inguinal and femoral lymph nodes after which Poupart's ligament was split and the dissection was continued retroperitoneally to remove the lymph nodes in the external iliac group, as is done in the classical groin dissection. The subcutaneous fat and deep fascia were then removed exposing the underlying muscles of the abdominal wall and chest, and the axillary lymph nodes, fat, and areolar tissue were removed from the left axilla. The wound was closed with interrupted black silk sutures without grafting. Multiple drains were inserted. Convalescence was uneventful.

Pathologic Report.—Malignant melanoma with metastasis to one inguinal lymph node. Twenty-five other nodes from the inguinal and axillary groups were examined microscopically and no metastatic foci were found in any of them.

TABLE I. COMPARISON IN FREQUENCY OF LOCAL RECURRENCE OF MALIGNANT MELANOMAS AND SQUAMOUS-CELL CARCINOMAS OF THE SKIN FOLLOWING SURGICAL REMOVAL

DIAGNOSIS	SKIN OF HEAD AND NECK			SKIN OF TRUNK			SKIN OF UPPER EXTREMITY			SKIN OF LOWER EXTREMITY		
	NO.	RECURRENCES		NO.	RECURRENCES		NO.	RECURRENCES		NO.	RECURRENCES	
		NO.	PER CENT		NO.	PER CENT		NO.	PER CENT		NO.	PER CENT
Squamous-cell carcinoma	30	5	16.7	24	3	12.5	12	2	16.7	3	0	0.0
Malignant melanoma	30	9	30.0	18	4	22.2	11	3	27.3	8	3	37.5

Conclusion: Melanomas of the skin invariably recur with greater frequency than squamous-cell carcinomas following surgical removal, regardless of the anatomic site.

REFERENCES

1. Adair, Frank E., and Pack, George T.: Melanomes sous-ungueaux et leur diagnostic differenciel, Bull. Assoc. franc. p. l'étude du cancer 19: 549-566, 1930.
2. Pack, George T., and Livingston, Edward M.: Treatment of Pigmented Nevi and Melanomas. In Pack, George T., and Livingston, Edward M.: Treatment of Cancer and Allied Diseases, Vol. 3, Chap. CXXII, New York, 1940, Paul B. Hoeber, Inc., pp. 2071-2094.
3. Pack, George T., and Adair, Frank E.: Subungual Melanoma; Differential Diagnosis of Tumors of the Nail Bed, SURGERY 5: 47-72, 1939.
4. Pack, George T., and Rekers, Paul: The Management of Malignant Tumors in the Groin; Report of 122 Groin dissections, Am. J. Surg. 56: 545-565, 1942.

VIRILISM IN WOMEN

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INTRODUCTION

IN VIEW of the physical and mental changes to which the syndrome of virilism may give rise, the condition is clinically and psychologically most striking. Although it may also be encountered in children, the ensuing remarks will be restricted to the syndrome in adults.

The symptoms and signs of virilism may be classified in two main groups: (1) those strictly defeminizing and (2) those which are considered masculinizing. Hermaphroditism may, on occasions, be associated with a picture of virilism. Fundamentally, the two conditions are distinct. In hermaphroditism a true congenital malformation is present, whereas in virilism it is essentially a question of transformation in an otherwise normal person prior to the onset of the syndrome.

Our attention was drawn particularly to this unusual picture on the occasion of encountering a case, described more fully elsewhere.¹ Subjected to surgical treatment, the patient made an uneventful recovery and showed regression of the symptoms of virilism afterward. This was a case of arrhenoma of the ovary. These tumors, which are comparatively rare, are not the only etiologic factor to be sought. Lesser grades of virilism without apparent clinical importance have also been observed. Pathologic studies of these cases, as well as the increasing knowledge gained in recent years about hormones and active biologic bodily chemical substances, have considerably increased our understanding about them and likewise permitted the use of new procedures to establish the diagnosis.

The defeminizing symptoms and signs are generally the first to appear. They include cessation of the menses, atrophy of the breasts and endometrium, and sterility. The masculinizing signs and symptoms are more numerous than the former, of wider distribution, and do not always completely recede. This is especially true in hypertrophy of the clitoris. These signs may be conveniently grouped according to the system affected. Thus, there are dermal, skeletal, vocal, muscular, and mental changes. Among the dermal alterations, increased pigmentation has been mentioned although the change in hair distribution is more prominent. It affects that of the face, breasts, abdomen, and lower extremities. A loss of the normal feminine curves probably ascribable to changes in the distribution of the body fat might be included here. Such is not the case of increase in the width of the shoulders or in the gait and contours of the neck and lower extremities, more reasonably linked with changes in the musculoskeletal system. The increased width of the shoulders is observed in cases of long duration, where there is, in addition, alteration in the distribution of the body fat and at times loss of weight. The change in voice with the assumption of a masculine tone is often an early manifestation. In our case this was so. The patient's husband no longer recognized her voice over the

telephone. Mental or psychic changes range from loss or reduction of the libido to alteration of the patient's character. It may also contribute to the masculine facial expression assumed by some.

In the case which came to our attention,¹ ascribable to arrhenoma, there was first increased growth of hair of the lower extremities. This gradually assumed a faunlike distribution, including the buttocks. Also, the hair on the skin of the upper lip became more prominent. The month following that in which the initial symptoms occurred, the menses failed to appear, except for a spotting for a few days several months after the initial amenorrhea. The amenorrhea itself persisted until after operation. Still another month later, hair appeared on the sides of the face, and this compelled the patient to shave once or twice a week. At this time the voice assumed a masculine tone. The pubic hair increased in amount and extended to the abdomen in masculine fashion. On admission, one and one-half years after the onset of the symptoms, hirsutism was also observed on the breasts. No skeletal changes were apparent. In addition, prominent hypertrophy of the clitoris was noted and the uterus was a bit small. A mass approximately the size of a large orange could be palpated in the right iliac fossa and right vaginal fornix on bimanual examination.

The tumor, which replaced the ovary, was excised together with the tube on the same side. Recovery was uneventful and the patient was discharged on the fourteenth postoperative day. The menses came on again one month later and appeared regularly thereafter just as before the onset of amenorrhea one and one-half years before. At examination six months after the operation, the voice was feminine, there was practically no hirsutism, the libido had returned, there were no apparent psychic changes from the normal, and the patient had gained ten pounds. The clitoris remained slightly larger than normal.

ETIOLOGY

All details pertaining to this case seem to indicate that the arrhenoma was responsible for the picture of virilism. This finds additional support in disappearance of symptoms after excision of the tumor. Arrhenomas are the ovarian tumors generally associated with the syndrome of virilism in women. The term itself has been coined to emphasize the common trait of their biologic activity and is preferred by Ewing² to the designation of arrhenoblastoma, introduced by Meyer.³ Among these tumors some are highly differentiated pathologically, as was the first to be described by Pick⁴ one of the so-called tubular testicular adenomas. Pick's case and those similar to it stand at one extreme of the scale, in contrast with the others, which constitute the undifferentiated or sarcoma-like group. Our case was of the latter variety. A detail as yet unexplained in the relationship which exists up to a certain degree between the various members of the arrhenoma group and the extent and intensity of the clinical features lies in the fact that certain ovarian tumors, which histologically correspond to the arrhenomas microscopically, have been found in the absence of any signs of virilism, as is also true for the inverse.⁵ Virilism has been reported in association with luteomas and hypernephromas of the ovary, and in a less pronounced manner also in the presence of a newly described affection of the ovaries designated diffuse ovarian luteinization.⁶ Because of the discrepancy in the pathologic picture and in the clinical features of some arrhenomas, exception has been taken to the indistinct use of this term to include them.

The adrenal glands, too, play an outstanding role as an etiologic factor in virilism in women. We are indebted to Cahill and collaborators⁷ for clarifying

considerably this phase of the etiology of virilism. It has been definitely linked with tumors of the gland associated with an increased production of androgens. These authors explain that in general the various clinical pictures to which tumors of the gland may give rise vary according to the hormones secreted, their amount, and the age and sex of the person affected.

After puberty and before the menopause, the adrenogenital syndrome is produced. It is manifest by the appearance of male secondary sex characteristics and the repression of female characteristics and function. This has also been called adrenal virilism.⁸ Hirsutism is the first change noted and this is followed by irregularity or cessation of the menses, changes in the body contour, and enlargement of the clitoris. Its occurrence is not infrequent and from an analysis of many cases, it has been found that the anatomic condition of the gland often bears no definite relation to the type or severity of symptoms.⁷ Tumors are cited as not a frequent cause. Loss of libido and its inversion have also been reported. The change of voice to a masculine type, frequently observed, is ascribed to lengthening of the vocal cords. Changes in the secondary sex organs appear later than menstrual or dermal alterations, although the younger the woman the more pronounced they are. In the young the tendency is toward underdevelopment; in the old, toward atrophy.

The changes associated with excess androgens excreted in the urine are also in direct proportion to the biologic effects produced. This increased excretion may be far above that excreted normally by man.

Certain doubt has been cast regarding the part the hypophysis may play in producing virilism. This is based on observations gathered from different sources. When arrhenoma may be excluded, hyperplasia or adrenal cortical neoplasia is to be favored. Of ten cases which came to autopsy reported by Geist and Gaines,⁶ seven were cortical adrenal adenomas and three adrenal carcinomas. In all cases the ovaries were small or normal in size with little evidence of follicular activity. These findings are also confirmed by the authors cited, in a review of the literature wherein similar cases were found and in which complete necropsies were performed.

The possible role, on the other hand, of certain thymic tumors in the etiology of virilism is denied by Silver,⁹ inasmuch as adrenal cortical hyperplasia with a normal pituitary has coincided and may not reasonably be excluded.

On the other hand, there is a suggestion that it may indirectly produce virilism through its action on the ovaries. Experiments in mice and in human beings with gonadotropins¹⁰ lend support to this view, as well as a case of basophilic adenoma with diffuse ovarian luteinization reported by Bergstrand.¹⁰

PATHOLOGY

From the remarks previously made, pathologic considerations will necessarily be restricted to the ovarian changes and those of the adrenals. In the case of some neoplasms of the adrenal glands reported to date, the element of outstanding interest to the clinician, frank malignancy of the tumors is generally recognized. It is an outstanding example of the outdated question as to whether malignant tumors might simultaneously be capable of secreting active biologic substances comparable to hormones. Hyperplasia or adenomas do not naturally bring up this question of malignancy. The extent and severity of the symptoms to which they may give rise, on the other hand, become important determining factors on contemplating a radical surgical therapeutic measure.

In the case of the ovaries, the malignant nature of the neoplasms seems more complex. In the histologically undifferentiated types the appearance of those which present a sarcoma-like structure is rather one of malignancy. The inverse is true, however, for the differentiated varieties in which tubular testicular structures are reproduced morphologically closely akin to those observed in the testicle. Generally speaking, the malignancy of this group of tumors as a whole is considered on the attenuated side. Yet frank recurrence has been observed on several occasions. In reference to this question the observations of Novak convey a warning as to the logical restraint which must still be observed.¹¹ He points out quite pertinently that in view of the rare occurrence of these cases, publication has preceded a wide enough interval of observation to judge adequately on this point.

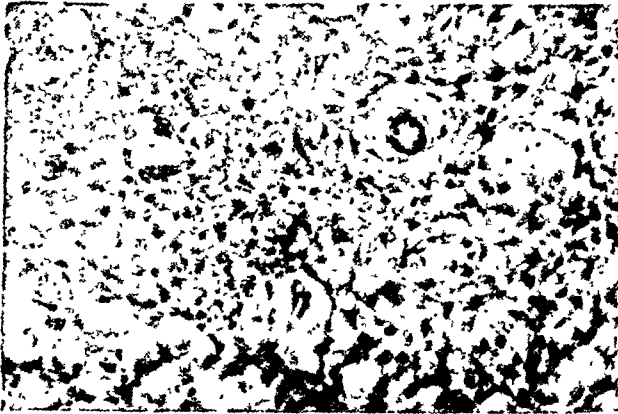


Fig. 1.—Photomicrograph of tumor.

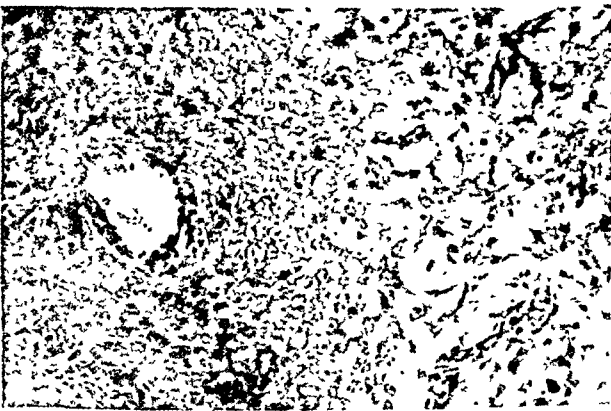


Fig. 2 —Photomicrograph of tumor.

To the surgeon and the clinician who have to contemplate the possibility of appropriate treatment, the size both of the adrenal gland or of the ovary assumes considerable practical importance. The adrenal enlargement may not be sufficiently pronounced to diagnose correctly and that of the ovary may be essentially imperceptible when the tumor occupies only part of the gland and may be of considerably reduced dimensions. These cases, however, are the exception rather than the rule. According to Marchand and Fibiger, adrenal enlargement from cortical hyperplasia may increase to the size of the kidney.¹² Adenomas, too, may reach considerable proportions, weighing as much as two or four ounces.² In adrenal carcinoma, Ewing² states that the earlier tumors

are smaller and embedded in the enlarged adrenal gland, the outline of which may be partly retained. He further states that at autopsy they are found to be large, involving the entire gland, adherent to or fused with the kidney, and bound to neighboring structures by many extensions.

Arrhenomas are, in general, of moderate size.⁵ The largest as yet observed was about the size of a man's head. The testicular adenoma is the one which tends to be small, firm, and well encapsulated.⁵ The others are larger and generally unilateral. Secondary changes may also be encountered in them as well as in the adrenal tumors. Since these may be considered as intrinsic pathologic alterations, no further mention will be made of them except for the case of hemorrhage or necrosis which may be safely presumed to give rise to local signs or even slight elevation of temperature.

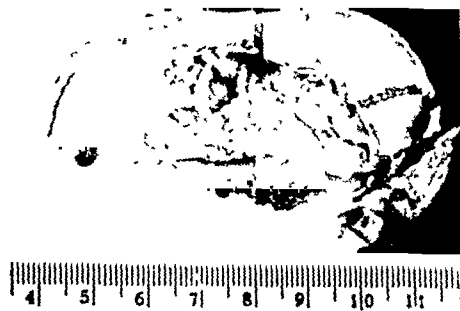


Fig. 3.—Gross aspect of part of tumor already fixed, showing cystic cavity.

DIAGNOSIS

Inasmuch as increased androgen excretion in the urine has been reported in cases of arrhenoma¹³ as well as in those of virilism associated with adrenal neoplasia or hyperplasia,⁷ the use of this estimation appears as yet only of limited value. In cases in which the adrenal gland is the site of neoplasia or sufficiently pronounced hyperplasia which may bring about a noticeable increase in its volume, periglandular air insufflation following the technique introduced by Cahill and associates⁷ prior to making a roentgenogram of the region has in such cases proved of definite diagnostic value. Certain reserve in assuming too dogmatic an attitude in reference to the cause is, however, advisable. Ovarian enlargement from some arrhenomas is hardly perceptible. On the other hand, it may be prominent, as was pointed out previously. Moderate enlargement has also been observed in diffuse ovarian luteinization, in which case conservative therapy is advisable. Although we ignore the association of other ovarian tumors or arrhenomas with cortical adrenal changes conducive to virilism, the possibility of encountering such cases would seem to warrant routine radiologic study of the lumbar region in virilism with preceding periglandular air insufflation.

The references to the investigation of androgenic urinary elimination which we have had occasion to consult are limited. It may be that more detailed studies in this field are necessary in an effort to determine any possible qualitative or quantitative differences which might prove of specific diagnostic value. Besides the special investigations which may be pursued in these cases, those obviously pertaining to the history and physical examination may add considerable weight to the diagnosis when metastasis is associated with an adrena-mass or when a definite ovarian tumor is palpated.

been definitely reduced; and in order to evaluate the results which have been obtained by the use of chemotherapeutic agents and other methods of therapy, this study was undertaken.

The patients with ruptured appendicitis admitted to the Charity Hospital in New Orleans in 1933 and in 1943 were studied and analyzed. These two years were chosen, a decade apart, because in the former group no sulfonamide drugs were employed, no attention was paid to plasma proteins, and gastrointestinal decompression was inadequately used, whereas in the latter group sulfonamide drugs were used in 97.5 per cent of the cases, plasma or blood was administered in 45 per cent, and decompression was employed in 88 per cent of cases. It is of interest that the incidence of ruptured appendicitis as compared with the total hospital admissions has definitely decreased in the Charity Hospital as determined by this study (Fig. 1). In 1933 there were 55,437 total hospital admissions, among which there were 156 cases with ruptured appendicitis, a percentage of 0.28. In the year 1943 there were 42,105 total hospital admissions, among which there were 83 cases with ruptured appendicitis, a percentage of 0.19. This decrease in the relative incidence of ruptured appendicitis probably is

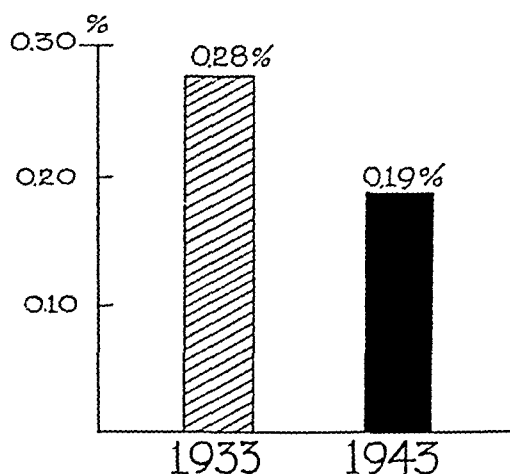


Fig. 1.—Diagram showing the incidence of appendical peritonitis in relation to total hospital admissions in Louisiana Charity Hospital in New Orleans.

due to the education of the laity and of the medical profession so that earlier diagnoses are made, and the patients are referred to the hospital before rupture has occurred. That catharsis is still a prominent factor in the production of appendical rupture is evidenced by the comparison of the two series. In the 1933 group of 81 cases, in which it was stated whether or not the patient had received catharsis, there were 73 cases (90 per cent) in which it was administered. In the 1943 group of 51 cases, in which it was stated whether or not catharsis was given, 46 patients received catharsis, with an identical incidence of 90 per cent.

Following rupture of the vermiform appendix, one of three complications can occur, depending to a certain extent upon the time that the patient is seen and operated upon. Immediately after the rupture, unless there has been an overwhelming infection and extensive contamination, there will result a localized peritonitis. If it remains localized, it will either resolve or will form a localized abscess. In

the presence of an overwhelming infection, or as the result of continued catharsis, or when produced by extremely virulent organisms in an individual whose resistance is diminished, a spreading infection and generalized peritonitis will occur. In the 1933 group of 156 cases, 52 patients had a localized peritonitis (33.3 per cent), 45 a localized abscess (29 per cent), and 57 (36.5 per cent) had generalized peritonitis, whereas in the 1943 group of 83 cases, 29 (35 per cent) had localized peritonitis, 33 (40 per cent) had localized abscess, and 21 (25 per cent) had generalized peritonitis (Fig. 2). It is thus seen that the incidence of localized peritonitis is about the same in both groups, and that the incidence of localized abscess increased in the latter period from 29 to 40 per cent. The exact cause for this increase is not clear, but would indicate a delay in the admission of the patient to the hospital and may be the result of the treatment of these patients at home with sulfonamide drugs by their physicians without a diagnosis being made. It is gratifying that the incidence of generalized peritonitis in the latter series is less, 25 per cent as compared with 36.5 per cent, which may also reflect the use of sulfonamide drugs before the patient is admitted to the hospital. Unfortunately, it was impossible for us to ascertain from the records of these patients whether or

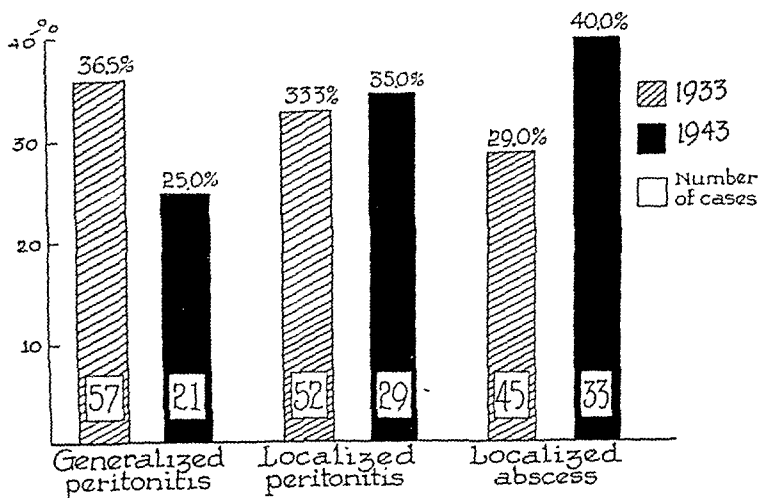


Fig. 2.—Diagram showing the type and incidence of peritoneal involvement in the patients with ruptured appendicitis admitted to the Charity Hospital in 1933 and in 1943.

not sulfonamide drugs had been used, although in many instances it was stated that the patient had been given some medication by his physician.

The duration of the symptoms before treatment, that is, before admission to the hospital, is interesting; and, although there is no particular difference in the two groups of cases, the 1933 and the 1943 periods, there is considerable difference in the types of peritoneal reaction (Fig. 3). In the cases with localized peritonitis in the 1933 series, the duration of symptoms before treatment varied from one to eight days, with an average of 3.2 days. In the 1943 series it varied from one to seven days with an average of 3.1 days. The average from the two groups was 3.1 days. In the group of cases with generalized peritonitis in the 1933 period, the duration of symptoms before treatment varied from twelve hours to seven days with an average of 3

days. In the 1943 period, it varied from one to fourteen days, with an average of 3.8 days. The average for both groups was 3.4 days. In the cases with localized abscesses, the duration of symptoms before treatment was definitely longer, as might be expected, because sufficient time must elapse before an abscess can develop. In the 1933 period, the duration varied from two to twenty-one days with an average of 9 days. In the 1943 period, it varied from one to thirty days with an average of 9.3 days. The average for both groups was 9.1 days.

Although it was not stated in all records whether or not the patient was acutely ill, the statement was given in 94 of the 1933 cases, of which 68 patients (72.3 per cent) were described as acutely ill. In 65 of the 1943 cases, a statement was made concerning the patients' appearance. Of these, 38 (67 per cent) were described as acutely ill. This suggests that the patients in 1933 were somewhat more ill at the time of admission to the hospital than those of the later group. That this contention is not correct is evidenced by a breakdown of the figures for the different types. In patients with localized peritonitis

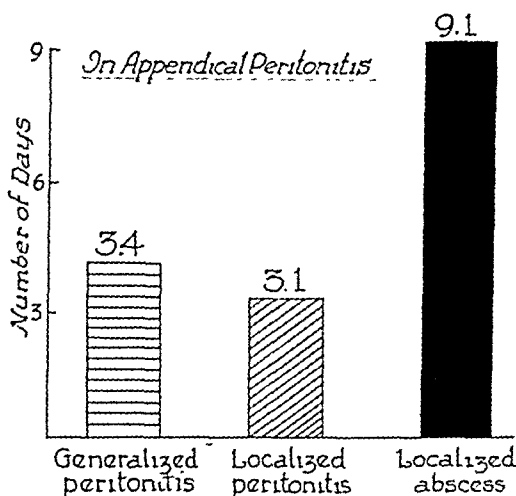


Fig. 3.—Diagram showing the duration of symptoms in the patients with ruptured appendicitis admitted to the Charity Hospital, according to the type of peritoneal involvement.

in 1933, for instance, 51.2 per cent were described as being acutely ill at the time of admission as contrasted with 75 per cent in the 1943 period. Also in the cases of generalized peritonitis, 90.4 per cent of the patients in the 1933 period were described as acutely ill as compared with 94.7 per cent in the 1943 group. In the cases with localized abscess there was a definite difference between the two groups since 62.0 per cent of the patients appeared acutely ill in the 1933 period as contrasted with 33 per cent in the 1943 group. Combining the two periods, it was found that 57 per cent of those with localized peritonitis appeared to be acutely ill, of those with localized abscess, 47 per cent, and of those with generalized peritonitis, 91 per cent.

The temperature and pulse readings did not vary significantly in the two periods. As might be expected, the mean averages in the cases with generalized peritonitis were higher than in the cases in which the infection was localized in the right lower quadrant.

The physical findings varied according to the type of peritoneal involvement. Tenderness was generalized in 27 per cent of the cases with localized peritonitis, in 23 per cent of the cases with localized abscess, and in 80 per cent of the cases with generalized peritonitis (Fig. 4). The point of maximum tenderness was in the right lower quadrant in 91 per cent of the patients with localized peritonitis. It is of interest that in this group of cases the point of maximum tenderness was in the right lumbar or flank area in 4 cases, in the region of the umbilicus in 1, and in the left lower quadrant in 2. In the patients with localized abscess, the right lower quadrant was the point of maximum tenderness in 95 per cent of cases. Interestingly enough it was in the region of the umbilicus in one case and in the right flank in 2 cases. In the cases of generalized peritonitis the point of maximum tenderness was in the right lower quadrant in 95 per cent, in the left lower quadrant in 2 cases, and below the umbilicus in 1 case. Whereas generalized rigidity is usually accepted as a sign of general peritonitis

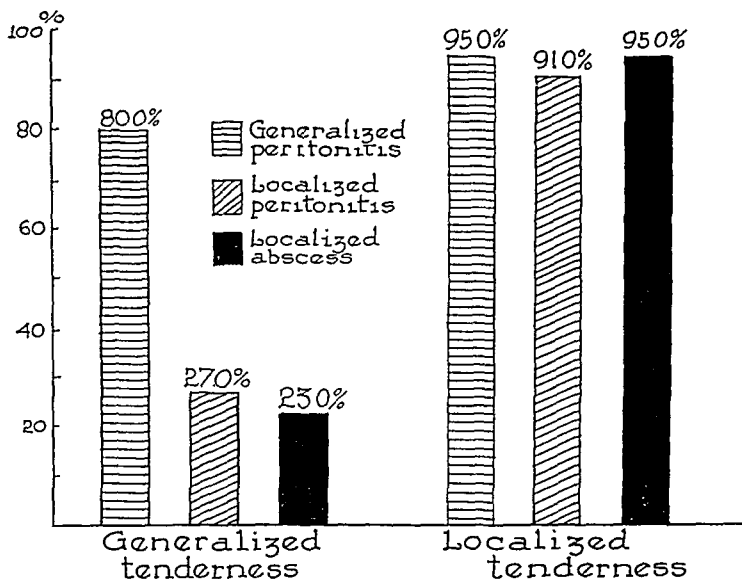


Fig. 4.—Diagram showing the incidence of generalized and localized tenderness in the various types of appendicular peritonitis.

and was present in 72 per cent of our patients, such is not always the case, because in 20 per cent of the cases of localized peritonitis and in 15 per cent of the cases with localized abscess, this finding was present. Rigidity in the right lower quadrant was present in 90 per cent of the cases with localized peritonitis, in 83 per cent with localized abscess, and in 94 per cent with generalized peritonitis (Fig. 5). Abdominal distention can occur either in generalized or in localized infections. It was present in 40 per cent of the cases with localized peritonitis, in the same number of cases with localized abscess, and in 86 per cent of cases with generalized peritonitis.

Seventy-five per cent of the patients with localized abscess had a palpable mass (Fig. 6). This was located in the right lower quadrant in 86 per cent of cases, in the cul-de-sac of Douglas in 10 per cent, in the right flank in 2 per cent, and in both lower quadrants in 2 per cent. A palpable mass was present in 17 per cent of the cases with localized peritonitis and in 97 per cent with generalized peritonitis.

The laboratory findings in all the groups of cases of ruptured appendicitis were approximately the same, there being little difference in the various series. The leucocyte counts in the cases with localized peritonitis varied from 6,000 to 35,000, with an average of 15,900 and an average polymorphonuclear count of 84 per cent. In the cases with localized abscess they varied from 4,000 to 35,000, with an average of 15,300 and an average polymorphonuclear count of 83 per cent. In the cases with generalized peritonitis these respective figures were 4,000 to 32,500; 15,100 and 86 per cent. It is evident, therefore, that the leucocyte and Schilling counts are not reliable in determining the extent of peritoneal involvement.

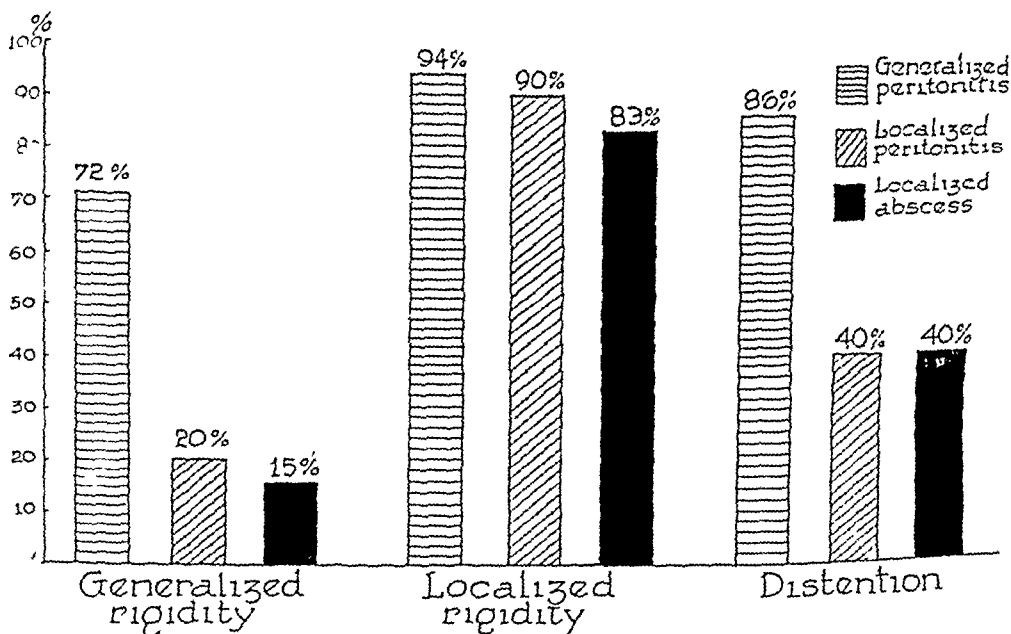


Fig. 5.—Signs of appendical peritonitis.

The therapy in the 1933 and the 1943 periods varied considerably. In 1933, a large number of cecostomies were done. In fact, 50 per cent of the patients with localized peritonitis complicating ruptured appendicitis had a complementary cecostomy (26 of 52 cases), and another had an ileostomy. Eight had appendectomy alone, 4 had appendectomy and cecostomy, 18 had appendectomy, cecostomy, and peritoneal drainage. None were treated conservatively. In the 1943 series, of which there were 29 cases, 24 had appendectomy alone, 1 had appendectomy and peritoneal drainage, 1 had appendectomy and freeing of adhesions, 1 had drainage of the peritoneal cavity alone, and 2 were treated conservatively, initially. In generalized peritonitis the number of cases in which cecostomy was used in 1933 was even higher than those with localized peritonitis. Of the 57 cases, cecostomy was done 51 times, appendectomy 55, peritoneal cavity drainage instituted in 49, and no operation was performed in 2. In 21 cases of generalized peritonitis in the 1943 group, 14 patients had an appendectomy, 1 had peritoneal drainage, and 6 had no operative procedure on admission. Of 45 patients with localized abscess treated in 1933, 3 had an appendectomy alone on admission, 13 had appendectomy and drainage, 20 had peritoneal drainage alone, 3 had appendectomy and comple-

mentary cecostomy, 3 had appendectomy, cecostomy, and peritoneal drainage, and 3 had nothing done. Of 33 patients treated in 1943, 11 had appendectomy alone on admission, 3 had appendectomy and peritoneal drainage, 1 had appendectomy and freeing of adhesions, 9 had peritoneal drainage alone, 3 had explorations leaving the inflammatory mass undisturbed, and 6 were not operated upon.

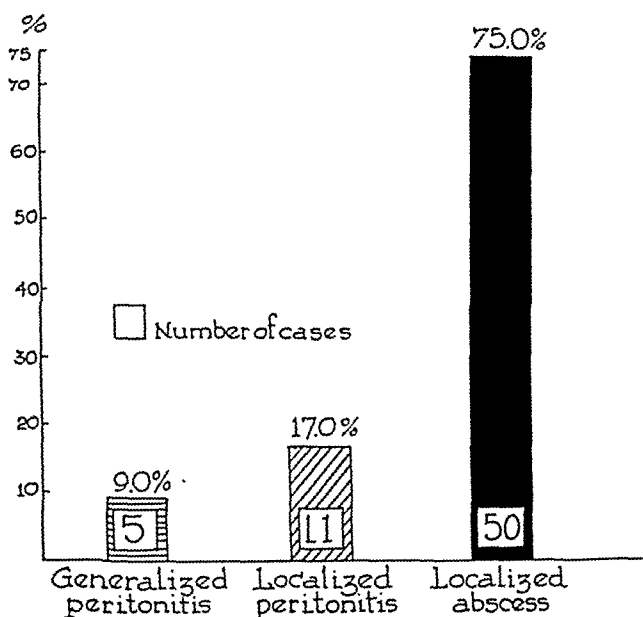


Fig. 6.—Diagram showing the incidence of palpable localized mass in various types of appendical peritonitis. Although this finding is present in generalized peritonitis and in localized peritonitis in a small group of cases, it is particularly important in those cases with a localized inflammatory mass in which conservative treatment is particularly indicated.

The postoperative treatment varied considerably in the two series of cases. Whereas the use of Fowler's position, the heat tent, morphine, and parenteral fluids varied little in the 1933 and the 1943 series, sulfonamide drugs, oxygen, blood, and plasma were employed much more frequently in 1943 than in 1933, in fact none of the patients in the 1933 cases received any sulfonamide drugs (Figs. 7 and 8).

The postoperative complications consisted generally of wound infection, residual peritoneal infection, ileus, and pulmonary lesions. In the patients with localized peritonitis, 11 per cent of those in the 1933 series developed subsequent residual infection, whereas 21 per cent in the 1943 series developed the same complication. In patients with localized abscess, this complication occurred in 18 per cent of the 1933 series and in 15 per cent of the 1943 group. In those with generalized peritonitis, the complication occurred in 23 per cent of the 1933 series and 10 per cent of the 1943 series. Because of inadequate description in the earlier cases, little could be determined concerning the incidence and extent of postoperative ileus and, therefore, a comparison of the two groups is not possible. The distinct impression is gained, however, that the almost routine use of the indwelling duodenal catheter and Wangensteen suction has decreased materially the incidence and severity of adynamic ileus.

The incidence of pulmonary complications in localized peritonitis was 9 per cent in the 1933 series and 7 per cent in the 1943 (Fig. 9).

This complication occurred in localized abscess in 6.8 per cent in 1933 and in none in 1943. It complicated generalized peritonitis in 12 per cent of the 1933 series and 10 per cent of the 1943 series. Forty-two per cent of all the pulmonary complications were right lower lobe pneumonias which probably were the result of an atelectasis produced by splinting of the right diaphragmatic leaf.

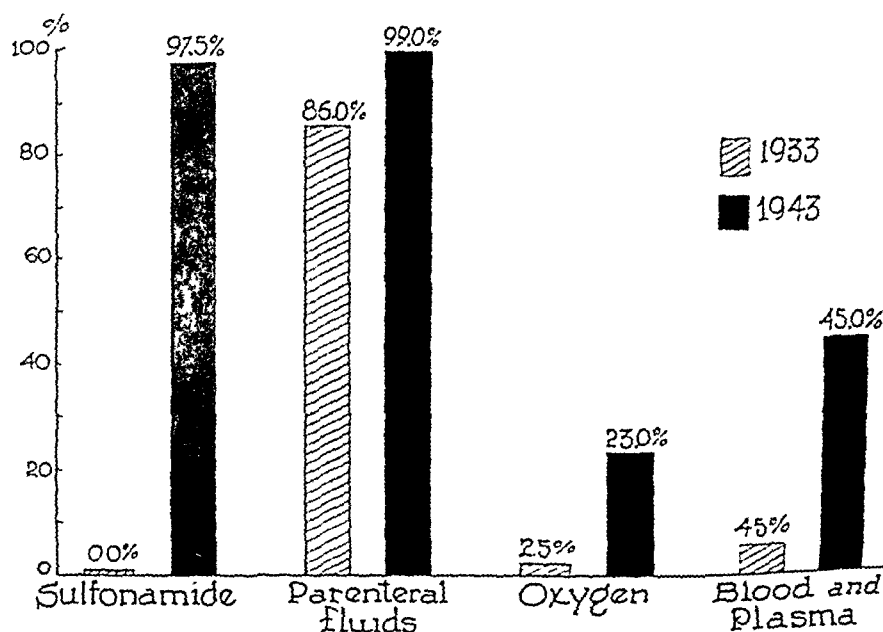


Fig. 7.—Postoperative therapeutic measures used in appendical peritonitis.

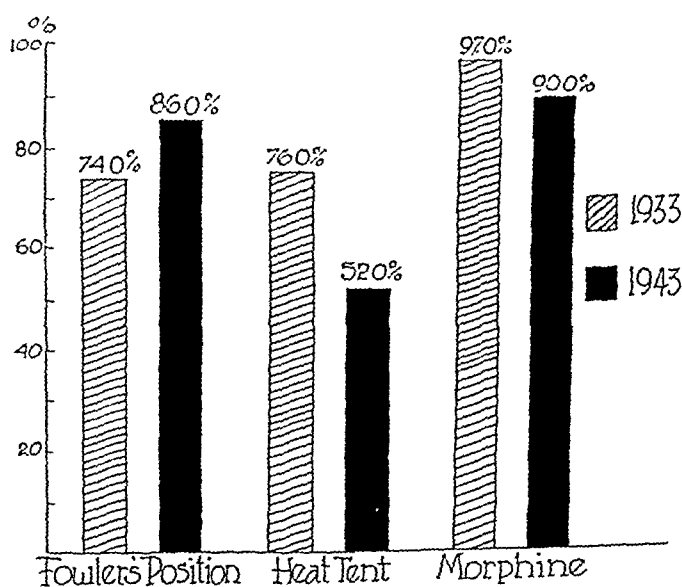


Fig. 8.—Postoperative therapeutic measures used in appendical peritonitis (continued).

The therapy used today is more effective than that employed in 1933, as evidenced by the decreased morbidity (Fig. 10) and mortality (Fig. 11). In the patients with localized peritonitis, the average hospital stay in the 1933 series varied from 8 to 119 days, with an average of 30.3 days, whereas in the same group of cases in the 1943 series the hospital stay varied from 8 to 72 days, with an average of 18.

The hospital stay in the cases with localized abscess in the 1933 group varied from 8 to 64 days, with an average of 27.9, whereas in the 1943 series these respective figures were 4 to 52, or 20.7. In generalized peritonitis, the average stay in the hospital varied from 13 to 81 days in the 1933 series with an average of 38.2, whereas in the 1943 group it varied from 9 to 98 days with an average of 26.1. An attempt was made to contrast the morbidities in the two series by determining the periods of pyrexia but no significant difference was found.



Fig. 9.—Incidence of pulmonary complications in appendical peritonitis.

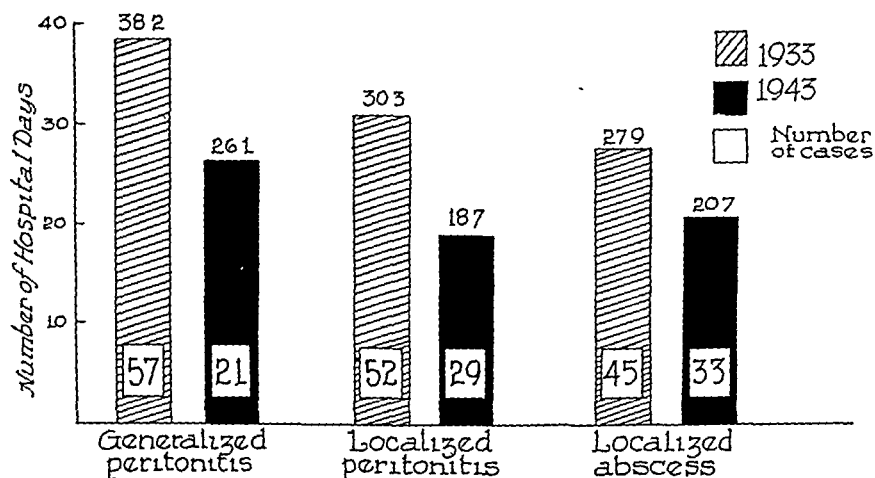


Fig. 10.—Diagrammatic representation of the average duration of the hospital stay in various types of appendical peritonitis.

A comparison of the mortality rate in the two groups of cases is of interest and significance (Fig. 11). In the Charity Hospital series there is a rather large number of patients who were moribund upon admission and who died shortly after admission. Since no form of therapy is successful in these cases, we have excluded from the analysis those dying within the first twenty-four hours; 8 of these were in the 1933 series and 7 in the 1943 group. The combined mortality rate in all types of appendical peritonitis in the 1933 series was 15 per cent

and in the 1943 series was 5.2 per cent. In the group of patients with localized peritonitis in 1933, there were 7 deaths in the 52 cases, a mortality rate of 13.4 per cent. In the 29 patients with localized peritonitis admitted in 1943, there were no deaths. In the cases with localized abscess, the mortality rate in the 1933 group was 6.8 per cent as contrasted with the mortality rate of 6 per cent in the 1943 group. In the cases with generalized peritonitis, the mortality rate in the 1933 group was 23.5 per cent, whereas in the 1943 group it was 14.2 per cent. It is evident that the mortalities both in the localized and in the generalized peritonitis groups were less in the 1943 than in the 1933 series, whereas there is no significant variation in the mortality rates with localized abscess in the two series. The improvement in the mortality statistics in the more recent cases with localized and with generalized peritonitis is due in part at least to the use of sulfonamide drugs since these chemotherapeutics are known to be of value in invasive infections. The lack of improvement in the mortality statistics in the more recent cases with localized abscess is probably due to the ineffectuality of the sulfonamide drugs in localized suppurative processes. This is well appreciated by most physicians at the present time, and these statistics demonstrate the necessity of instituting drainage of localized collections of pus before sulfonamide drugs can be effectual. As has been shown repeatedly, the presence of para-aminobenzoic acid and other sulfonamide inhibitors in purulent exudate and necrotic tissue nullifies the action of the sulfonamide drugs.

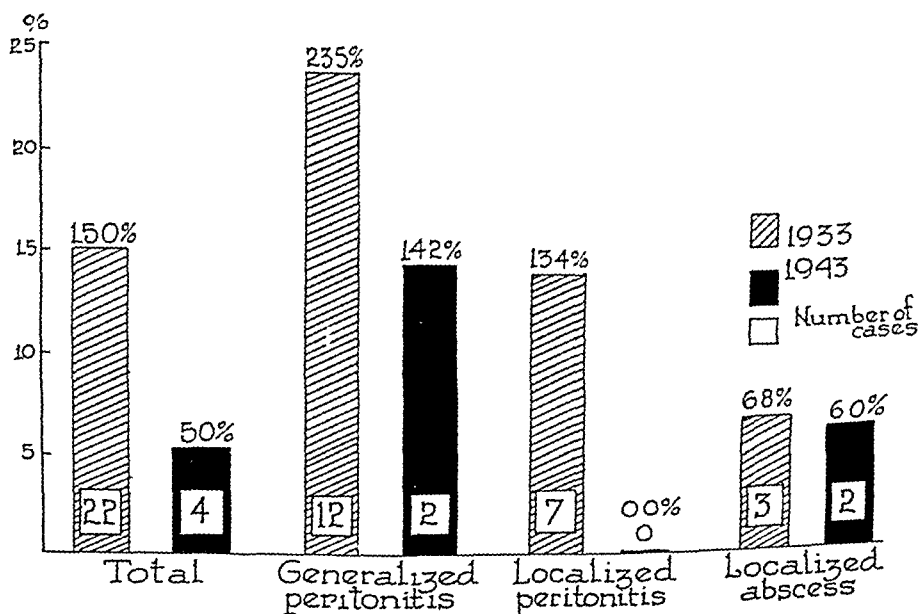


Fig. 11.—Diagrammatic representation of the mortality in appendicular peritonitis

Whereas the progressive decrease in the morbidity and the mortality rates at the present time in appendicular peritonitis might be attributed by many to the use of sulfonamide drugs, and whereas undoubtedly those chemotherapeutic agents do exert a beneficial effect upon the invasive infections of the peritoneal cavity, it is our belief that not all the credit can be given to these substances. That the mortality rate in acute suppurative appendicitis can be affected beneficially by the

sulfonamide drugs was demonstrated by the results of Ravdin, Rhoads, and Lockwood,⁴⁰ who showed that they were able to decrease the mortality rate from 1.5 per cent in these cases to 0.4 per cent in a series of cases in which sulfonamide drugs were given orally and parenterally. Dees¹¹ was probably the first to use sulfonamide drugs intraperitoneally in cases of perforated appendicitis and reported good results by this method of administration. The local implantation of sulfonamide drugs has been used since 1940 at the Roosevelt Hospital in New York. Thompson, Brabson, and Walker⁴⁹ reported in 1941 that in a series of 51 cases of appendical abscess and appendical peritonitis in which sulfonamide drugs were used there were no deaths, as contrasted with 0.78 per cent and 11.2 per cent, respectively, in a series of 166 cases in which chemotherapy was not used. The beneficial results from the use of sulfonamides in the treatment of peritonitis is attested by many reports.^{1, 2, 8, 12, 13, 16, 17, 20-23, 26, 29, 30, 38, 41, 44-46, 48, 52, 53}

There is no uniformity of opinion concerning the way in which sulfonamide drugs should be used or which of them should be employed. Since the original use of the sulfonamide drugs intraperitoneally by Dees¹¹ and the popularization by Thompson and his co-workers⁴⁹ at the Roosevelt Hospital in New York, many have used sulfonamide drugs intraperitoneally and there has been considerable experimentation on both the effectiveness in and the effects of sulfonamides in the peritoneal cavity. Throckmorton⁵⁰ studied the peritoneal reactions to various sulfonamide compounds and found that in addition to the bacteriostatic effect of the sulfonamides, they probably are beneficial in peritonitis by increasing the local cellular mechanism. There was a considerable variation in the amount of cellular reaction produced, the reaction varying from a slight response of the peritoneum to sulfanilamide, to the very marked reaction produced by sulfapyridine. He considers sulfathiazole to be the ideal agent for intraperitoneal use since it is specific against a large number of microorganisms, it is relatively innocuous to the peritoneum, it has a prolonged bacteriostatic effect, and it stimulates some local peritoneal response, similar to any other form of peritoneal vaccination. Walter and Cole,⁵¹ from experimental work on animals, came to the conclusion that sulfadiazine was the best sulfonamide to administer intraperitoneally. They noted that the blood level following the intraperitoneal administration of sulfadiazine was higher than when sulfanilamide was used. Rosenberg and Wall,⁴² from their experimental work, suggested the use of sulfanilamide in the peritoneal cavity. Laufman and Wilson²⁵ were able to protect rats from peritoneal infection by the intraperitoneal use of sulfanilamide. Tashiro, Pratt, Kobayashi, and Kawaichi⁴⁶ recommend the local implantation of sulfanilamide in cases of peritonitis and report good results as observed both clinically and experimentally. Others who have advocated the use of sulfonamide drugs intraperitoneally are Gardiner,¹⁶ Elman and Eckert,¹² Estrin,¹³ Hudson and Smith,²⁰ Kinney,²³ Lee,²⁶ McGehee,²⁹ Presnell,³⁸ Ravdin, Lockwood, and Rhoads,³⁹ Rea,⁴¹ Smyth,⁴⁴ Thompson, Brabson, and Walker,⁴⁹ Tether,⁴⁸ Wellborn and Stubblefield,⁵³ Jackson and Collier,²¹ Ryan, Bauman, and Mulholland,⁴³ and Laird and Stavern.²⁴ On the other hand, there are many who are of the opinion that sulfonamide drugs should not

used locally in the peritoneal cavity. Harvey, Meleney, and Rennie,¹⁹ from their experimental studies, came to the conclusion that sulfonamide drugs, especially sulfathiazole, were efficacious in protecting against peritonitis, but were more efficacious when given systemically than when given intraperitoneally. Lesses and Starr²⁷ report 2 patients with toxic manifestations following intraperitoneal use of sulfonamide drugs. Jackson and Collier²¹ have reported similar cases and state that there was an increase in the incidence of jaundice in cases in which sulfonamide drugs were used intraperitoneally. In the 2 cases reported by Lesses and Starr,²⁷ anemia, leucopenia, and hepatitis resulted from a single injection of sulfanilamide intraperitoneally. In the first case a fatality resulted, but probably not because of the effects of the sulfanilamide. Loeb²⁵ reports a case of severe systemic toxic effect produced by the intraperitoneal implantation of sulfanilamide, which resulted in severe hepatitis and marked anemia. Taylor⁴⁷ warns against the use of the sulfonamide drug in wounds, particularly in clean wounds, and questions whether it should ever be put in the peritoneal cavity even though there may be contamination. Whereas we have used sulfonamide drugs, particularly sulfanilamide crystals, locally in the peritoneal cavity in cases with definite contamination, we now believe that there is little advantage in administering sulfonamide drugs in this manner and that this practice may be actually detrimental. We now prefer the intravenous administration of sodium sulfadiazine in these cases.

The beneficial effects of the use of chemotherapeutic agents in diffuse peritonitis in childhood are illustrated by the following figures. Alford,¹ in reporting the cases from the Hospital for Sick Children in Toronto, showed that the mortality rate from appendical peritonitis in 1935 was 64 per cent; in 1936, 76 per cent; in 1937, 43 per cent; in 1938, 40 per cent; in 1939, 21 per cent; and in 1940, there were no deaths. Stafford⁴⁵ had a mortality of 10 per cent in 489 patients with appendical peritonitis and abscess who were treated without the use of sulfonamide drugs, whereas in 105 in whom sulfonamide drugs were used, there were 5 deaths, a mortality of 4.76 per cent. Wattenberg and Heinbecker,⁵² reporting the cases from the St. Louis Children's Hospital, had 27 deaths in 164 cases of appendical abscess and peritonitis (16.4 per cent). In a group of 46 similar cases in which sulfonamide drugs were used, there were 5 deaths, a mortality rate of 10.8 per cent. These same authors, in the cases of generalized peritonitis, had a mortality rate of 38.1 per cent before the use of sulfonamide drugs, as contrasted with 15.6 per cent following the introduction of sulfonamide therapy, and a mortality rate of 9.02 per cent in the patients with localized abscess who were treated before sulfonamide drugs, and no fatalities in the group in which sulfonamide drugs were used.

As previously mentioned, one is likely to give credit for the improvement in results in recent years entirely to sulfonamide drugs. That such is not wholly the case, we are convinced by our own series. Undoubtedly, a great deal is being accomplished by the use of supportive measures, particularly the use of plasma and whole blood and the prevention of hypoproteinemia with resultant improvement in wound

healing, and the rapid establishment of water balance. Bower and his co-workers^{5, 6} have emphasized the importance of the use of plasma in cases of peritonitis and recommend giving it in every case in which there is a perforated appendicitis. Elman and Eckert¹² have warned against the use of parenteral fluids in patients who have a hypoproteinemia because of the danger of producing a salt edema. In these cases it is particularly important to give plasma. Collier⁷ has recently emphasized the danger of the indiscriminate use of saline solutions. In our own series, the administration of plasma and blood has undoubtedly been of great value in decreasing the morbidity and the mortality.

The use of decompression, either by means of an indwelling duodenal catheter with Wangensteen suction or with the double tube (Miller and Abbott), is of great importance, because unquestionably many of these patients die and many of them continue to have symptoms because of the associated ileus (Fig. 12). Probably of great value also in decompressing the gastrointestinal tract is the administration of high concentrations of oxygen, as originally suggested by Fine and his co-workers.¹⁴ In our own series, the use of both of these therapeutic measures has undoubtedly done a great deal, not only to increase the comfort of the patients with appendical peritonitis, but also to decrease the morbidity and mortality.

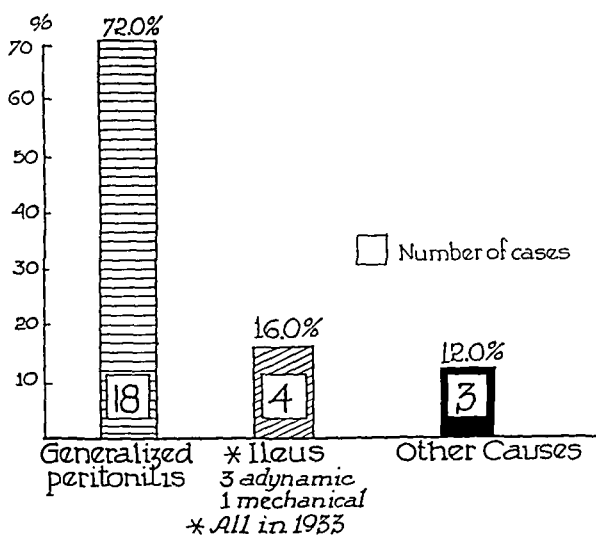


Fig. 12.—Diagrammatic representation of the causes of death (1933 and 1943) in appendical peritonitis excluding the moribund cases in which the patient died within twenty-four hours of admission.

It is now quite generally agreed that unless there is a localized abscess, peritoneal drainage not only does no good, but actually may be harmful. The incidence of postoperative complications and residual infections is actually higher when peritoneal drainage is instituted in cases of nonlocalizing processes than when peritoneal drainage has not been done. Cottis¹⁰ reports 97 cases of perforated appendicitis with frank peritonitis, of which drainage was done in 54, with a mortality of 24 per cent. In another group of 43 cases in which drainage was not done, there was a mortality rate of 9.5 per cent. Elman and Eckert¹² are of the opinion that drainage is much less necessary now than before the use of the sulfonamide drugs. On our own serv-

Drainage of the peritoneal cavity is never instituted unless there is a definite, localized abscess or an unremoved localized necrotic area. It is not even used in a localized peritonitis because it is our opinion that one cannot drain the peritoneal cavity per se, and the introduction of a foreign body into the peritoneal cavity produces trauma which tends to cause more adhesions resulting in possible residual infections and intestinal obstruction. On the other hand, if a definitely walled-off process is encountered, drainage of that area can and should be done.

Even though drainage of the peritoneal cavity is not done, it is imperative that drainage of the abdominal wall be used. Whereas we originally sutured the abdominal wall in layers and inserted a rubber tissue drain deep to the fascia, bringing it out one end of the wound, we now employ the delayed closure of the skin and subcutaneous fat as advocated by Gamble,¹⁵ Collier and Valk²⁰ and Lee.²¹ This latter method consists of suturing the peritoneum and fascia at the time of the operation. Deep sutures are inserted through the skin, down to and through the fascia, but are left untied. The wound is packed with gauze for twenty-four to forty-eight hours, after which time the gauze is removed and the previously placed sutures are tied, thus approximating the skin and subcutaneous tissue. In this way, phlegmons of the abdominal wall and progressive infection can be prevented, healing by primary intention being obtained in many instances.

Whereas the treatment of appendicitis is always immediate extirpation of the appendix as soon as the diagnosis is made, there are some cases of appendical peritonitis in which the complicating peritonitis is of more importance than the originating appendicitis. Although the late A. J. Ochsner,¹¹ who advocated the conservative treatment of appendical peritonitis, spoke of the conservative treatment of appendicitis, he never practiced such therapy, but he did advocate and practice the conservative treatment of appendical peritonitis. If, in a given case, there is any question about rupture of the appendix, immediate operation is indicated because as previously emphasized, the *only* treatment of acute appendicitis per se is appendectomy. Also, if there is any question concerning the presence of localization, operation is indicated, because in the absence of localization, the removal of the offending appendix can be done without materially increasing the risk and the focus from which the emanating infection is thus removed. The conservative treatment of appendical peritonitis is indicated *only* in those cases in which localization of the infective process has taken place. This can be determined with considerable difficulty at times and unless there is a definite palpable mass indicating localization, exploration is probably indicated in all cases. In some of these cases without a definite palpable mass which are explored, and in which a well-localized inflammatory process is found at operation, the mass should be left undisturbed and a drain placed down to the mass. The rationale for the conservative treatment of appendical peritonitis is based upon the fact that following peritoneal trauma, a reaction of the peritoneum occurs which tends to wall off the traumatizing agent (Figs. 13 and 14). In the case of bacterial peritonitis, the walling off of the infected process is extremely desirable; and, if in the be-

ginning of the walling off process and for a few days thereafter, the patient is operated upon and the protective adhesions separating the focus from the rest of the peritoneal cavity are broken down with spread of the highly infective organisms and their toxins into an un-

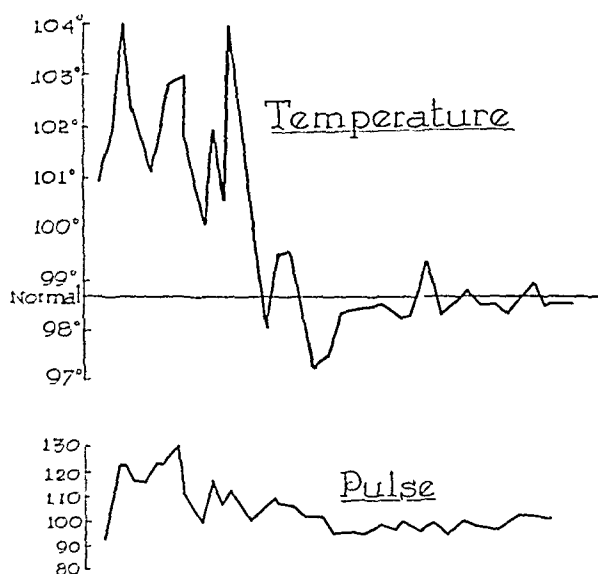


Fig. 13.—Diagrammatic representation of a clinical chart of a patient admitted with a ruptured appendicitis and localized right lower quadrant inflammatory mass which had been present for four days. Under conservative therapy there was prompt resolution of the inflammatory process, permitting discharge of the patient from the hospital on the tenth day. Patient subsequently returned for appendectomy.

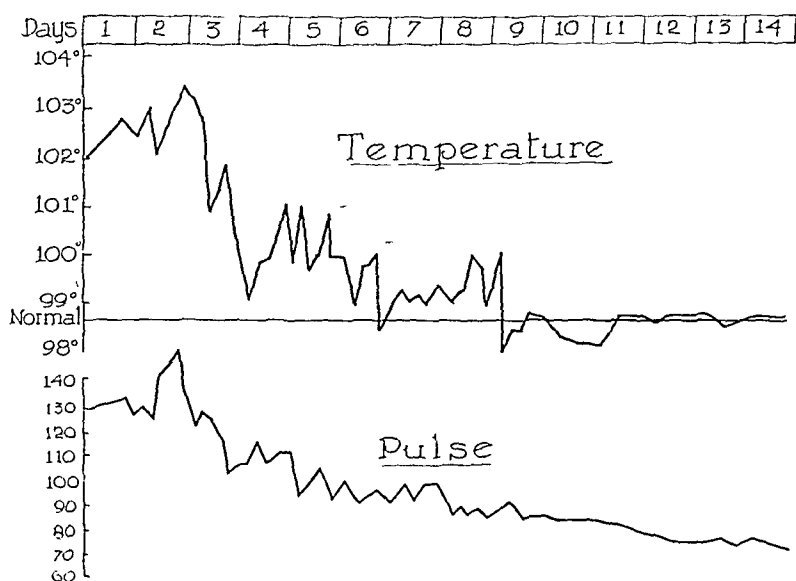


Fig. 14.—Diagrammatic representation of clinical chart of patient with ruptured appendicitis. Patient had been sick two days before admission to hospital. At the time of admission, there was a localized right lower quadrant inflammatory mass. Patient was treated conservatively with gradual resolution of the inflammatory process and subsidence of clinical manifestations. He was discharged on the fourteenth day to return later for an appendectomy.

involved portion of the peritoneal cavity, an overwhelming toxemia is likely to result. If, on the other hand, the conservative treatment, which consists of the withholding of everything by mouth, the use of the indwelling duodenal catheter, and the administration of large doses

Appendical Abscess Treated Conservatively: Simple Drainage Would Have Been Preferable

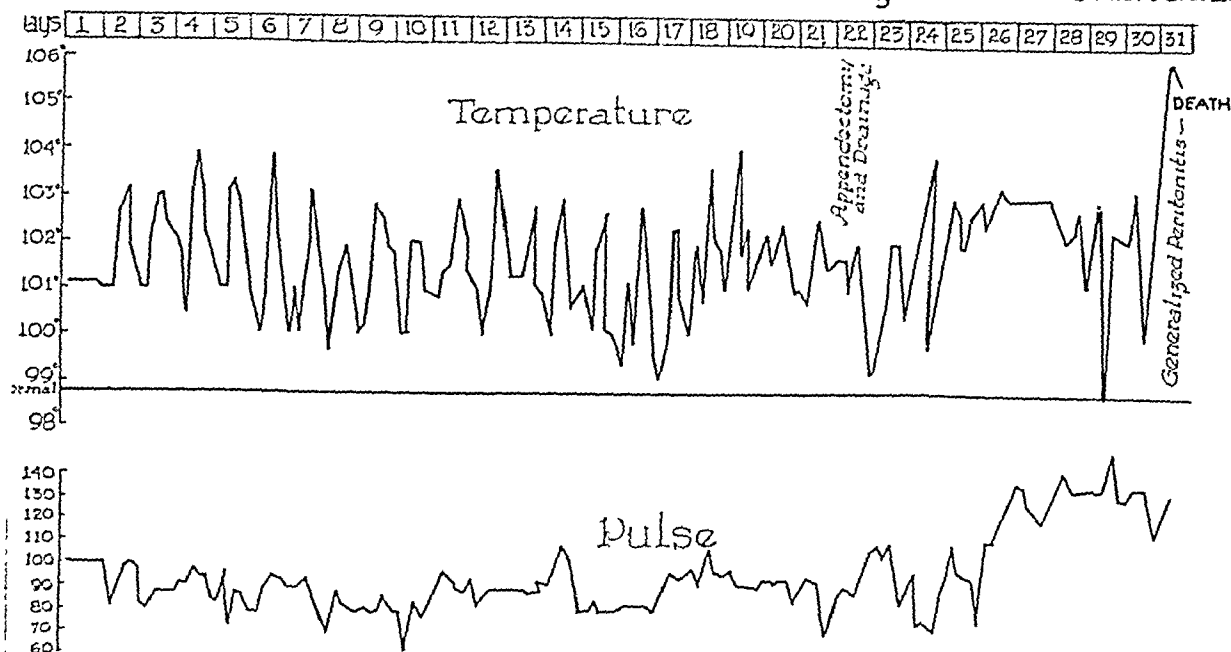


Fig. 15.—Diagrammatic representation of clinical chart of patient admitted three weeks after onset of symptoms consisting of chills, fever, and diarrhea. On admission, a large nontender mass was palpable in the right flank. Patient was treated conservatively without a diagnosis being made, and probably much too long. On the twenty-second day abdominal exploration was done through the free peritoneal cavity. An abscess was opened and an appendectomy done. This resulted in extension of the infection to the uninvolved portion of the peritoneal cavity, with generalized peritonitis and death. Undoubtedly simple drainage of the abscess should have been done in this patient much earlier, which would have prevented the tragic outcome. The conservative treatment in this instance was indicated but was incorrectly executed.

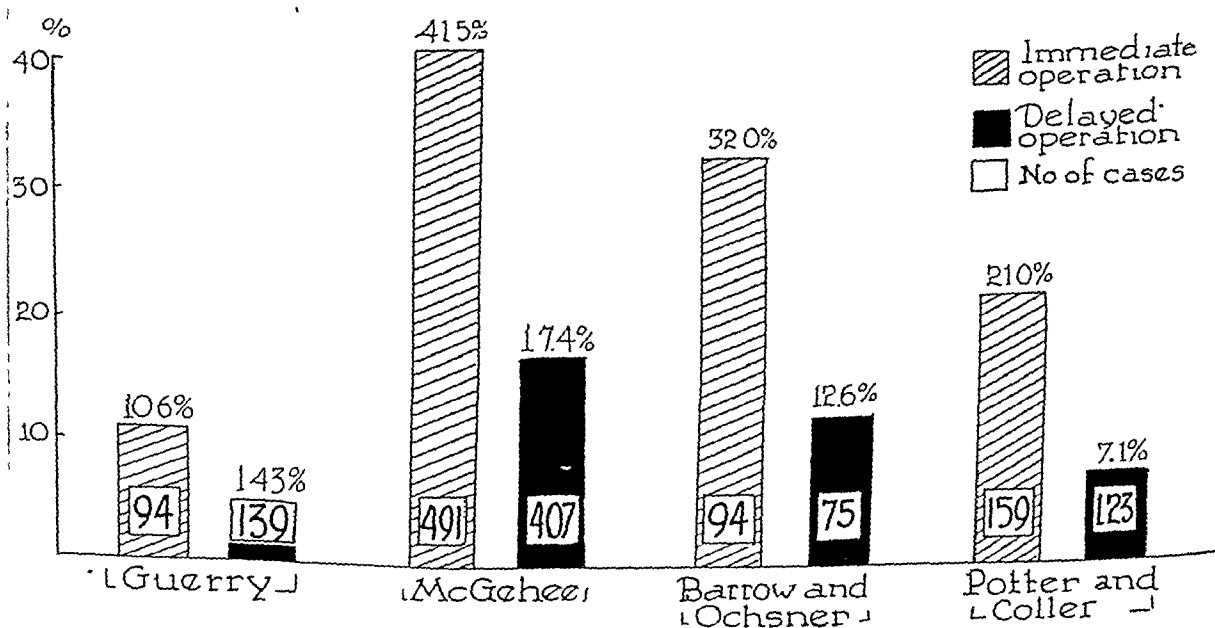


Fig. 16.—Diagrammatic representation of the value of the conservative treatment of appendical peritonitis as obtained by different clinicians.

morphine, the application of heat to the abdomen, Fowler's position, and the administration of parenteral fluids and subcutaneous drugs, is instituted, localization of the process can occur so that subsequent drainage of the abscess can be done without danger. Although it has been argued that the complication incidence is higher following the conservative treatment of appendiceal peritonitis than when immediate operation is done, irrespective of the time the patient is seen, this is no valid objection to the treatment. From our own experience we are convinced that the complication incidence is definitely higher in those cases in which appendiceal peritonitis has been treated conservatively, because these patients live long enough to develop their complications. Also these cases are more difficult to handle in that they require the employment of keener surgical judgment and more careful supervision than any other type of surgical patient. It has often been stated that no one can determine what is going on in the peritoneal cavity, and for this reason the conservative treatment of appendiceal peritonitis is never justified. Certainly if there is no evidence of localization, or if there is any question about whether localization has occurred or not, operation is indicated. This is particularly true in young individuals and in older persons in whom localization is not as likely to occur as in young adults. If, however, at the time of operation a localized mass is found with the inflammatory process walled off, the adhesions should not be broken down and the appendix removed. In such an instance, a rubber tissue drain should be placed down to the mass and the abdominal wall closed around it. Whereas considerable fortitude is required to do nothing more than this in a patient with a ruptured appendix, it is undoubtedly lifesaving in many instances.

In the conservative treatment of appendiceal peritonitis, it is imperative that constant supervision be maintained in order to determine whether the process is progressing or subsiding. If there is any evidence of progression, incision and drainage in such a way as to prevent opening an uninvolved portion of the serous cavity are imperative in order to prevent extension into the free peritoneal cavity (Fig. 15). In the cases treated conservatively, about three-fourths will subside spontaneously without going on to abscess formation. In the remaining 25 per cent it will be necessary to drain the abscess and in all cases a subsequent appendectomy must be done, because with very few exceptions another attack of appendicitis is likely to occur.

The value of conservative treatment of certain cases of appendiceal peritonitis is shown by Fig. 16.^{3, 4, 18, 29, 37}

SUMMARY AND CONCLUSIONS

1. Despite an appreciable decrease in the incidence of appendiceal peritonitis in the past decade, this complication remains all too frequent and calls for constant and further emphasis both to the laity and to the medical profession in order to obviate this disaster which is, almost without exception, preventable.
2. Our statistics show that cathartics are administered in 90 per cent of cases of ruptured appendicitis, which is indeed deplorable.
3. Appendiceal rupture is usually associated with the development of one of three complications depending on many co

controllable factors: localized peritonitis, localized abscess (or, more correctly, walled-off inflammatory process), and spreading or generalized peritonitis.

4. Comparison of treatment and results in the years 1933 and 1943 indicates that therapy now employed is more effective than that used formerly. The use of sulfonamide drugs has been a boon in lowering mortality and morbidity; equally important, however, are the use of relatively large amounts of blood and plasma and the routine employment of gastrointestinal decompression in all cases with any possibility of adynamic ileus.

5. A statistical analysis is given of the various findings in the different types of appendical peritonitis. The presence of a palpable mass is of considerable importance in the diagnosis and in governing subsequent therapy; it is indicative of walling off and localization. Such cases are included in the so-called "localized abscess" group just mentioned. A more accurate and descriptive term for this group would be localized inflammatory process.

6. A plea is made for careful study and individualization in every case of appendical peritonitis. In a given case we advocate:

- (a) Immediate surgical extirpation of the vermiform appendix in all cases of unruptured appendicitis.
- (b) Immediate appendectomy in all patients with ruptured appendicitis in whom there is not definite and demonstrable localization. Thus, we believe in immediate appendectomy in the localized and generalized peritonitis cases of the diffuse type.
- (c) Conservative therapy of all cases of localized inflammatory processes. This treatment consists essentially of obtaining absolute rest of the gastrointestinal tract by withholding everything by mouth, liberal use of morphine, application of external heat to the abdomen, gastrointestinal decompression by indwelling duodenal catheter or Miller-Abbott tube. In addition, liberal use of blood and plasma to avoid anemia and hypoproteinemia, sulfonamide drugs parenterally to control infection, and oxygen to aid in preventing distention, are important. In 75 to 80 per cent of such cases the inflammatory process will quickly recede; interval appendectomy should then be done at a later date. Twenty to twenty-five per cent will progress to localized suppuration and will require drainage; great care is absolutely imperative in avoiding uninvolved peritoneum in such drainage.

7. We believe the sulfonamide drugs do give an added factor of safety in dealing with appendical peritonitis; however, this factor should be used as a supplement to, rather than a replacement of, surgical judgment. Our studies convince us that localized inflammatory processes are best treated conservatively; there is no chemotherapeutic agent known which obviates the risk of a fulminating generalized peritonitis when immediate operation and appendectomy is practiced routinely on this group of patients.

REFERENCES

1. Alford, Kenneth M.: Prognosis and Treatment of Acute Diffuse Peritonitis Since the Advent of Chemotherapeutic Drugs, *Arch. Dis. Child.* 43, 1941.

2. Anderson, Robert K.: Sulfathiazole as an Adjunct to Surgery in Advanced Acute Appendicitis, *J. A. M. A.* 118: 892, 1942.
3. Barrow, Woolfolk: Appendiceal Peritonitis, *Kentucky M. J.* 39: 184, 1941.
4. Barrow, Woolfolk, and Ochsner, Alton: Treatment of Appendical Peritonitis, *J. A. M. A.* 115: 1246, 1940.
5. Bower, J. O., Terzian, L. A., Burns, J. C., Trachtenberg, H. B., and Pearce, A. E.: Appendiceal Peritonitis: Experimental and Clinical Investigations Into the Causes of the High Mortality, *J. A. M. A.* 118: 1284, 1942.
6. Bower, J. O., Terzian, L. A., and Pearce, A. E.: Changes in the Blood and the Composition of the Peritoneal Exudate in Induced Spreading Peritonitis, *Arch. Surg.* 44: 1091, 1942.
7. Coller, Frederick A., Campbell, K. N., Vaughan, H. H., Iab, L. V., and Moyer, C. A.: Postoperative Salt Intolerance, *Ann. Surg.* 119: 533, 1944.
8. Coller, Frederick A., and Singleton, Albert O., Jr.: Peritonitis, *Proc. Interst. Postgrad. M. A. North America*, p. 322, 1941.
9. Coller, F. A., and Valk, W. L.: Delayed Closure of Contaminated Wounds; Preliminary Report, *Ann. Surg.* 112: 256, 1940.
10. Cottis, G. W.: The Fallacy of Peritoneal Drainage, *Am. J. Surg.* 60: 204, 1943.
11. Dees, J. G.: A Valuable Adjunct in Perforated Appendices, *Mississippi Doctor* 18: 215, 1940.
12. Elman, Robert, and Eckert, C. L.: Treatment of Acute Perforative Peritonitis: Importance of Operation, Oxygen Inhalations, Plasma Transfusions and the Sulfonamides, *J. Missouri M. A.* 39: 193, 1942.
13. Estrin, Joseph: Intraperitoneal Application of Sulfanilamide in Peritonitis Complicating Appendicitis, *M. Rec.* 154: 189, 1941.
14. Fine, J., Sears, J. B., and Banks, B. M.: Effect of Oxygen Inhalation on Gaseous Distention of Stomach and Small Intestine, *Am. J. Digest Dis.* 2: 361, 1935.
15. Fine, J., Banks, B. M., Sears, J. B., and Hermanson, L.: Treatment of Gaseous Distention of Intestine by Inhalation of 95 Per Cent Oxygen; Description of Apparatus for Clinical Administration of High Oxygen Mixtures, *Ann. Surg.* 103: 375, 1936.
16. Gamble, Hugh A.: The Application of the Open Treatment of All Potentially Infected Abdominal Wounds and Results, *Mississippi Doctor* 21: 8, 1943.
17. Gardiner, R. H.: Intraperitoneal Sulphapyridine in Acute Abdominal Conditions, *Lancet* 1: 195, 1942.
18. Gottesman, Julius, and Goldberg, Harold: Acute Appendicitis With Generalized Peritonitis; Treated by Intravenous and Direct Intraperitoneal Injection of a Sulfonamide Derivative, *J. A. M. A.* 118: 207, 1942.
19. Guerry, LeGrand, and McCutchen, George T.: The Management of Appendiceal Peritonitis With Special Reference to the Operative Handling of the Localized Abscess, *Ann. Surg.* 115: 228, 1942.
20. Harvey, H. D., Meleney, F. L., and Rennie, J. W. R.: Peritonitis: III. Studies in Peritoneal Protection With Particular Reference to Action of Sulfonamide Drugs in Experimental Peritonitis, *SURGERY* 11: 244, 1942.
21. Hudson, Rupert Vaughan, and Smith, Rodney: Intraperitoneal Sulphanilamide; Its Prophylactic and Therapeutic Value, *Lancet* 1: 437, 1942.
22. Jackson, Howard C., and Coller, Frederick A.: The Use of Sulfanilamide in the Peritoneum; Experimental and Clinical Observations, *J. A. M. A.* 118: 194, 1942.
23. Jonas, A. F., Jr.: Sulfathiazole in the Treatment of Appendiceal Peritonitis, *Am. J. Surg.* 57: 112, 1942.
24. Kinney, C. A.: The Use of Sulfanilamide in the Peritoneum, *J. South Carolina M. A.* 37: 137, 1941.
25. Laird, George J., and Stavern, Herbert: Intraperitoneal Use of the Sulfonamides, *California & West. Med.* 56: 293, 1942.
26. Laufman, Harold, and Wilson, Catherine E.: Prophylactic Intraperitoneal Introduction of Crystalline Sulfanilamide; Experimental Observations, *Arch. Surg.* 44: 55, 1942.
27. Lee, Herbert Carl: The Treatment of Acute Appendicitis With Peritonitis, *Virginia M. Monthly* 69: 484, 1942.
28. Lesses, Mark Falcon, and Starr, Arnold: Toxic Effects From the Intraperitoneal Use of Sulfanilamide, *New England J. Med.* 226: 555, 1942.
29. Loeb, Martin J.: Systemic Toxic Effects Caused by Topical Application of Sulfanilamide in the Peritoneal Cavity, *New York State J. Med.* 43: 447, 1943.
30. McGehee, John Lucius: Advances in the Treatment of Acute Peritonitis of Appendiceal Origin, *Mississippi Doctor* 18: 488, 1941.
31. Mueller, Roland F.: Treatment and Results in Appendicitis, *Minnesota* 24: 243, 1941.
32. Ochsner, A. J.: A Handbook of Appendicitis, Chicago, 1902, G. P. Engel and Company.
33. Ochsner, Alton: The Conservative Treatment of Appendiceal Peritonitis, *Orleans M. & S. J.* 87: 32, 1934.
34. Ochsner, Alton: The Conservative Treatment of Appendiceal Peritonitis, *State J. Med.* 32: 579, 1937.

34. Ochsner, Alton, Gage, I. M., and Garside, Earl: The Intra-Abdominal Post-Operative Complications of Appendicitis, *Ann. Surg.* 91: 511, 1930.
35. Ochsner, Alton, and Lilly, George: The Technique of Appendectomy, *STURGERY* 2: 572, 1937.
36. Ochsner, Alton, and Murray, Sam: Appendicitis, *Am. J. Surg.* 46: 566, 1939.
37. Potter, E. B., and Collier, P. A.: The Treatment of Peritonitis Associated With Appendicitis, *J. Michigan M. Soc.* 32: 573, 1933; also *J. A. M. A.* 103: 1753, 1934.
38. Presnell, G. R.: Acute Appendicitis; Management of Rupture With Spreading Peritonitis, *J. Missouri M. A.* 40: 137, 1943.
39. Ravdin, I. S., Lockwood, J. S., and Rhoads, J. E.: The Results of Sulfonamide Prophylaxis in the Surgery of the Large Bowel, *S. Clin. North America* 22: 1585, 1943.
40. Ravdin, I. S., Rhoads, J. E., and Lockwood, J. S.: The Use of Sulfanilamide in the Treatment of Peritonitis Associated With Appendicitis, *Ann. Surg.* 111: 53, 1940.
41. Rea, Charles E.: The Use of Sulfonamides in Abdominal Surgery, *Minnesota Med.* 27: 99, 1944.
42. Rosenberg, S., and Wall, Norman M.: The Treatment of Diffuse Peritonitis by the Direct Intraperitoneal Introduction of Sulfanilamide, *Surg., Gynec. & Obst.* 72: 568, 1941.
43. Ryan, J. D., Bauman, Eli, and Mulholland, J. H.: The Blood Concentration With Urinary Excretion of Sulfadiazine, *J. A. M. A.* 119: 484, 1942.
44. Smyth, Calvin, Jr.: The Use of Sulfanilamide in the Management of Spreading Peritonitis of Appendiceal Origin, *S. Clin. North America* 22: 1611, 1942.
45. Stafford, Edward S.: The Value of Sulfathiazole in the Treatment of Peritonitis and Abscess of Appendiceal Origin, *Surg., Gynec. & Obst.* 74: 365, 1942.
46. Tashiro, K., Pratt, O. B., Kobayashi, N., and Kawauchi, G. K.: The Local Implantation of Sulfanilamide in the Peritoneal Cavity and Its Clinical Application in Peritonitis, *STURGERY* 11: 671, 1942.
47. Taylor, Frederic W.: The Misuse of Sulfonamide Compounds, *J. A. M. A.* 118: 959, 1942.
48. Tether, Russell K.: Treatment of General Peritonitis of Appendiceal Origin, *J. M. Soc. New Jersey* 39: 331, 1942.
49. Thompson, James E., Brubson, John A., and Walker, John M.: The Intra-Abdominal Application of Sulfanilamide in Acute Peritonitis, *Surg., Gynec. & Obst.* 72: 722, 1941.
50. Throckmorton, T. D.: The Peritoneal Response to Locally Implanted Crystalline Sulfonamide Compounds, *STURGERY* 12: 906, 1942.
51. Walter, LeRoy, and Cole, Warren R.: The Intraperitoneal Administration of Sulfadiazine: With Special Reference to a Comparative Study With Sulfanilamide, *Surg., Gynec. & Obst.* 76: 524, 1943.
52. Wattenberg, Carl A., and Heinbecker, Peter: The Treatment of Acute Appendicitis in Children as Influenced by Chemotherapy, *STURGERY* 12: 576, 1942.
53. Wellborn, Mel B., and Stubblefield, K. F.: The Intra-Abdominal Application of Sulfanilamide in Acute Perforative Appendicitis; Preliminary Report, *South. Surgeon* 11: 24, 1942.

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